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Scientists are rushing to figure out how the human microbiome influences a variety of health conditions.



[SECTION 1]

IN THE LAB

All signs are pointing toward a more personalized approach to disease prevention and treatment.

Where We Stand

Coming off a public health disaster and political and social upheaval during the pandemic, the medical field faces huge challenges. Still, advancements in artificial intelligence, genomic discoveries and the ability to harness the immune system are driving research and fueling hope. Here, some trends that are shaping the way we'll be thinking about wellness and care in the future.

By Janet Lee



LOSING YEARS

Life expectancy declined at its most significant rate in more than seven decades in 2020 and 2021, thanks to COVID-19. It now stands at 76.60 years on average, down from 78.86 in 2019, according to a study from the University of Colorado Boulder, the Urban Institute and Virginia Commonwealth University. While 19 other peer countries included in the report also saw declines in 2020—albeit less severe than the U.S. drop—they at least rebounded somewhat in 2021. Besides the pandemic, research also pointed to the obesity epidemic, heart disease and health care inequities for the widening gap between the U.S. and other countries. Of note: The largest declines in life expectancy in between 2019 and 2021 were among Black and Hispanic populations.

MIND MATTERS

Mental health has taken a nosedive over the last couple of years, but even before that 20% of adults experienced a mental illness, according to a 2022 report from Mental Health America (MHA). Thoughts of suicide are on the rise, and a significant portion of adults and youth don't receive or have access to treatment. One potential stopgap: Last summer, the new 988 Suicide & Crisis Lifeline went live (it was formerly known as the National Suicide Prevention Lifeline, reachable via a 10-digit phone number). Anyone having a mental health, substance use or suicide crisis can call or text 988 and speak to a real person instead of dialing 911 or going to the emergency room. To read more about the roots of the mental health crisis in the U.S. and promising research into psychedelics, *turn to page 60.*





PREPARING FOR CLIMATE EVENTS

A 2022 study published in Nature Climate Change *found that climate change can worsen 58% of all known pathogenic diseases. "The question becomes, how do we adapt to this new set of threats as a society?" says Amir Sapkota, chair of the epidemiology and biostatistics department at the University of Maryland School of Public Health. "It requires a paradigm shift in medicine and public health. Rather than simply reacting to these threats, we have to apply proactive approaches." For example, a high risk of heat waves and forest fires in an area could trigger early warning systems that tell doctors and clinicians providing dialysis to prepare for more patients that week (heat worsens kidney conditions), says Sapkota. For more on how climate change is impacting health,* *turn to page 78.*



CANCER CARE FOR ALL

The number of cancer survivors is expected to rise by about 30% between 2019 and 2030. "Where we are today is much better than where we were 20 years ago," says Dr. David Ryan, clinical director of the Massachusetts General Hospital Cancer Center in Boston. Oncologists are now better able to target various types of cancer, but that also means there's a need for specialists who are familiar with these specific subtypes and there aren't enough of those to go around, especially in rural areas, says Ryan. "The opening up of virtual care has created tremendous opportunities to reach out to more isolated communities," he says, but some states still don't allow it unless the doctor is licensed in that state (like Maine and New Hampshire). To read about some of the new advances in cancer treatment, *turn to page 44.*

A MYSTERIOUS ILLNESS

Long COVID—symptoms like brain fog, joint pain and heart issues—is baffling researchers and physicians. The National Center for Health Statistics estimates that 14% of U.S. adults have had long COVID. "We have to solve the puzzle that causes long COVID," says Dr. Ziyad Al-Aly, a clinical epidemiologist at Washington University in St. Louis. "Why are some people profoundly disabled and others are unscathed? We need to understand the mechanisms." Al-Aly is lead author of a pre-print study investigating the risks of COVID-19 reinfection. "Does [it] elevate your risk of various health problems [including death and hospitalization]? The answer is absolutely yes." This summer, the National Institutes of Health launched a study that will follow thousands of people, tracking their acute and post-COVID symptoms.





A SHARPER LENS

Scientists have relied on observational studies for years to investigate associations between things like alcohol intake and heart disease risk. The problem is, observational studies can't show that one thing causes another. There are also often confounding variables in the background that can affect outcomes. One example: Drinking a glass of wine a day is associated with a lower risk of heart disease, but is it the wine or other healthy habits, such as exercise or eating a plant-based diet? Thanks to the genetic data that scientists can now gather during a study, it's easier for them to test risk factors based on genetic variants and determine causation. The method is called Mendelian randomization and it's appearing in more and more studies. *To see how alcohol impacts heart disease, turn to page 73.*

REDEFINING "HEALTH"

"Traditionally a lot of the focus for heart health has been on things like blood pressure and quitting smoking, but now we're including social determinants of health as part of our guidelines," says Dr. Michelle A. Albert, president of the American Heart Association and a professor of medicine at the University of California, San Francisco. "For example, sleep impacts blood pressure and if you live in an environment where you're under stress, sleep quality is poorer. So you just can't tell people to get better sleep." The AHA is just one group that's investigating how social determinants of health, including racism; safe housing; clean water; healthy, affordable food; education; transportation and employment status together impact health outcomes, and how to include these factors in the data they collect and incorporate them into treatment.





MAKING PREGNANCY (AND BEYOND) SAFER

With 17.4 deaths per 100,000 pregnancies, the U.S. ranks at the bottom for maternal mortality among industrialized nations. Black women are two-and-a-half to three times more likely to die in or right after childbirth as white women and Hispanic women, according to a 2020 report from the Commonwealth Fund. "There's a lot of research in the area in terms of health care disparities and social determinants of health," says Dr. Joanne Stone, chair of obstetrics, gynecology and reproductive science at the Icahn School of Medicine at Mount Sinai in New York. "There's also a big emphasis on what's called the fourth trimester now, the postpartum period." (Forty percent of maternal deaths happen within six weeks after the day of delivery.) In addition, Stone says there's a push to make a patient's pregnancy history part of their overall medical history. "Things like preeclampsia increase risk for high blood pressure, stroke and heart disease later, but a lot of internal medicine doctors don't ask about that," she says. Read about efforts to improve equity in health care on page 88.

Janet Lee is a writer and editor in Kansas City, Missouri.



'THE LONG-AWAITED MALARIA VACCINE FOR CHILDREN IS A BREAKTHROUGH FOR SCIENCE, CHILD HEALTH AND MALARIA CONTROL.'

—Tedros Adhanom Ghebreyesus, PhD, WHO Director-General

Between 2020 and 2022, 12 countries were certified malaria-free by the World Health Organization, including China, Argentina, Morocco and Sri Lanka.

FROM THE *TIME* VAULT

9 Mid-Pandemic Discoveries

While most eyes have been on COVID-19, researchers have also made groundbreaking advancements in other fields.

By Jeffrey Kluger

1 THE *OTHER* BIG VACCINE NEWS

Public-health officials have long sought a vaccine against malaria, which infects up to 600 million people a year and kills 400,000, mostly children. In 2021, there was dramatic progress on this front. In October, the World Health Organization (WHO) approved the use of the RTS,S vaccine in children in sub-Saharan Africa or other areas of the world where malaria transmission is moderate to high.

In addition, in a study of 450 children in Burkina Faso, published in the *Lancet* in May 2021, researchers reported that a new malaria vaccine, called R21, is 77% effective—just clearing the World Health Organization's 75% efficacy standard.

The sample group for the study was comparatively small, though, and more research is needed. Investigators working for a multicenter international team, including the University of Oxford, plan to follow the initial sample group for longer and will conduct other trials in countries where malaria is active year-round, while also working to improve the immune response from the shot.



Hand-and-face transplant recipient Joe DiMeo tests out the strength of one of his new hands.

2 NEW FACE, NEW HANDS—NEW MAN

In summer 2020, a team of 16 surgeons and 80 operating-room staffers at NYU Langone Health performed the world's first successful face and double hand transplant, completing the procedure in just 23 hours. Speed is essential in transplant surgery, because the sooner that donor tissue is connected to the recipient's vascular system, the less time it is denied a blood supply.

The recipient was 22-year-old Joe DiMeo of Clark, New Jersey, who suffered third-degree burns over 80% of his body in a 2018 car accident. His fingertips had to be amputated, and damage to his face was so extensive that he was left without lips or eyelids—even after 20 reconstructive surgeries. In 2019, DiMeo was listed as a possible transplant recipient; 10 months later, a suitable face-and-hands donor was located. Only two other face-and-hand transplants have been attempted: In the first, the recipient died of complications from the surgery; in the second, the hands had to be amputated because of infection. Advanced computer modeling helped the surgeons plan the latest transplant, and 3D cutting guides assisted in sawing and aligning bones, as well as properly positioning the plates used to attach the donor tissue. Two years post-surgery, DiMeo still goes to occupational therapy and hopes to write a book.

3 AN OBESITY DRUG THAT ACTUALLY WORKS

A study published in March 2021 in the *New England Journal of Medicine* showed that the drug semaglutide—typically administered to treat Type 2 diabetes—can have powerful weight-loss effects. A



The brain needs time to clear out cellular debris, which may thwart inflammation.

sample group of 1,961 people with a body mass index of 30 or greater (the level considered "obese," though the scale has been criticized for overgeneralizing) were given either a weekly dose of 2.4 mg of semaglutide (the average weekly dose for diabetes treatment is 1 mg) or a placebo, coupled with lifestyle intervention like diet and exercise. At the end of a 68-week trial period, the semaglutide group lost an average of 14.9% of their body weight compared with 2.4% for the placebo group.

4 A CLEAR CONNECTION BETWEEN SLEEP AND DEMENTIA

Poor sleep duration has long been thought to be associated with Alzheimer's disease and other neurodegenerative conditions, but the cause-and-effect association is hard to establish, and studies typically don't run past 10 years or so, making it hard to track how sleep patterns play out over decades. In a robust study published in April 2021 in *Nature Communications*, a sample group of 7,959 people had their health and sleep patterns tracked throughout their 50s, 60s and 70s. The results were striking: Those who slept six hours or less per night had a 30% higher risk of developing dementia than those who slept seven hours. While depression and other mental-health disorders are thought to have a role in changes in sleep duration and increasing dementia risks, the investigators corrected for those variables and did not find them to be relevant in their findings. They also ruled out sociodemographic and cardiometabolic factors. Though the investigators did not say with certainty which mechanism connects short sleep cycles to the onset of dementia, they speculated that lack of sufficient sleep can be associated with neuroinflammation, atherosclerosis and poor clearance of amyloid protein—which makes up Alzheimer's plaques—from the body.

5 A GUT CHECK ON ALZHEIMER'S RISK

It's no secret that the human microbiome has a profound effect on overall health. Now research has gone further than ever before to establish that the trillions of bacteria and other microorganisms that live

in the gut may also play a role in the development of Alzheimer's disease. In a study led by researchers at the Istituto Centro San Giovanni di Dio Fatebenefratelli in Italy, investigators looked at lipopolysaccharides, proteins that are found on the membranes of gut bacteria that cause inflammation, as well as at certain short-chain fatty acids, some of which have neuroprotective effects. Using PET scans and blood tests of 89 people ages 65 to 85, the researchers found a higher incidence of amyloid plaques in the brains of those with higher levels of lipopolysaccharides and the bad fatty acids in their blood—and thus in their gut bacteria. Fewer plaques were found in those with the protective fatty acids. The findings point to the possibility of microbiota manipulation as a preventive for Alzheimer's.

6 PSILOCYBIN AND MDMA PROVE THEIR PSYCHOTHERAPEUTIC METTLE—AND PROMISE

Over the past year, psychoactives that had been mostly used as recreational drugs started really establishing themselves as frontline mental-health treatments. In an April 2021 study, published in the *New England Journal of Medicine*, 59 patients with depression were divided into two groups: One received psilocybin (aka psychedelic mushrooms); the other received escitalopram (a selective serotonin reuptake inhibitor) and a smaller dose of psilocybin. Both had therapy alongside the treatment. At the end of the six-week study period, those in the psilocybin group performed better on a self-rating depression survey than those receiving the escitalopram—though the difference was just shy of statistical significance. In an unrelated *Nature Medicine* study published in May 2021, 90 people suffering from post-traumatic stress disorder (PTSD) were similarly divided into two groups, one of which received three doses of MDMA—the active ingredient in ecstacy—plus talk therapy. The other received the therapy and a placebo. The conclusion: 67% of the people who had taken MDMA no longer met the criteria for a PTSD diagnosis, compared with 32% of the placebo group. Multiple startups are working to commercialize the use of psychoactives for therapeutic purposes. (For more on how psychedelics are being used for mental health, turn to page 64.)

7 THE FIRST HUMAN-MONKEY CHIMERA

In an April 2021 study published in the journal *Cell*, professor Juan Carlos Izpisua Belmonte, PhD, created an embryonic chimera that combined human and nonhuman primate cells, strictly designed for research purposes only, and engineered to be unable to advance beyond the embryonic stage. The research has two purposes. The first is to study the process known as gastrulation—the point two weeks after conception when embryonic cells begin to differentiate into the body's more than 200 cell types. The second goal is to help scientists develop better systems for growing tissues and organs—intended for transplantation into humans—in other animals, including pig embryos, which are seen as less ethically controversial and more accessible.



A handful of cities have decriminalized psilocybin and some states are moving to legalize it for medicinal purposes, with supervision.

8 BONE-MARROW TRANSPLANT CURES HIV

For blood-cancer patients who are not responding to chemotherapy, a bone-marrow transplant is sometimes an option. For three such patients so far—all part of the ongoing IMPAACT P1107 study—the transplant has proved to be a treatment for a second disease, too: HIV/AIDS. The patients each received cord blood stem cells that had a mutation in the CCR5 gene, which prevents HIV from effectively binding to cells. After the transplant, circulating HIV disappeared from the formerly positive patients' blood. The first patient was in remission for 12 years before dying of leukemia in September 2020. The second patient has been in remission for more than 30 months, according to the National Institutes of Health. As of February, a third transplant recipient has had no detectable levels of HIV for more than 14 months. However, the doctors involved stress that such transplants can carry more risk than simply staying on antiretroviral medications.

9 STOPPING DENGUE AT THE SOURCE

Dengue fever has had a free ride for too long. There is no effective vaccine or therapeutic against the mosquito-borne disease, which infects 50 million people per year—and in a warming planet, the dengue-carrying *Aedes aegypti* mosquitoes' range is spreading to include regions that typically had a low incidence of the disease. But a study led by the World Mosquito Program in the Indonesian city of Yogyakarta and released in August 2020 may point to a solution: Infect the insects with another pathogen—the *Wolbachia* bacterium—which prevents *Aedes aegypti* from spreading dengue when they bite humans. In the 27-month trial, Wolbachia-infected mosquitoes were released across Yogyakarta, and the result was a 77% reduction in dengue incidence. Investigators believe the strategy may also be effective in preventing other mosquito-borne viral diseases, including Zika, chikungunya and yellow fever. *—Updated excerpt from* TIME, *June 10, 2021*

Jeffrey Kluger is a TIME *editor-at-large.*

The Doctor Can Call You Now

PATIENTS HAVE FLOCKED TO TELEHEALTH, BUT POLICYMAKERS ARE SKEPTICAL.



Telehealth use exploded during the early days of the pandemic thanks to regulations the government and states relaxed during the public health emergency. Now telehealth companies and medical groups are pushing to make these pandemic-inspired shifts permanent.

Many of these changes are set to stay in effect into 2023, and the Center for Medicare and Medicaid Services (CMS) indicated that it will keep certain expanded Medicare telehealth services in place through December 2023. (State rules allowing interstate telehealth for non-Medicare patients vary, with many rescinding waivers that temporarily allowed it.)

While proponents of telehealth argue it improves access and convenience for patients, some policymakers still have questions about the quality of care telehealth can deliver, the cost of expanding it further and the potential for fraud in virtual care. (In July, the Department of Justice brought charges in a $1.2 billion telehealth fraud scheme.)

"This has changed our entire health care ecosystem forever," says Jacqueline Marks, a senior manager at Manatt Health. "I think everyone's just trying to figure out right now, how do we go forward?" *—Abigail Abrams*



So far the only approved vaccine for dengue is for children ages 9 to 16 who have already been infected in the past and who live in areas where it's endemic.



Adjusting electrical impulses in the body may help treat asthma, arthritis and even dementia.

FROM THE *TIME* VAULT

Bioelectronics Are Sparking New Hope

This rapidly evolving approach may eliminate the need for toxic drugs and give people back their lives.

By Alice Park



‘ELECTRICITY IS THE LANGUAGE OF THE NERVOUS SYSTEM, AND WE NEED TO LEARN HOW TO SPEAK IT.’

—Robert Kirsch, PhD

When the disease plaguing her digestive system was at its worst, Kelly Owens once had to rush to the bathroom 17 separate times in the course of a few hours. By the time she was 25, her crippling case of Crohn’s disease had given her arthritis from her jaw to her fingertips. The dozens of drugs she took helped a bit, but the brutal side effects included nausea, fatigue and weight gain. “My body was at war with me,” she says. Worse, the powerful drugs she took were weakening her bones: at 25 years old, she had the frail and weakened skeleton of an 80-year-old.

There is no known cure for Crohn’s, an inflammatory bowel disease that affects nearly 800,000 people in the U.S. Available medication provides only temporary relief. Owens, who was diagnosed at age 13, eventually developed resistance to all of the drugs she tried and doctors told her there was nothing left to explore.

Hope for Owens and millions of others experiencing a broad range of previously untreatable, or unsatisfactorily treated, diseases may be near, thanks to a breakthrough that seems more science fiction than medical reality. The remarkable convergence of advances in bioengineering and neurology has resulted in a fast-developing way to treat chronic diseases, known as bioelectronic medicine. These advances allow scientists to identify specific nerves and implant devices that can be activated when needed to stimulate or dial down their activity; that in turn controls cells in organs targeted by those nerves that regulate the body’s many immune and metabolic responses. While some bioelectronic, or electroceutical, therapies already exist to treat conditions such as headaches and certain cases of depression, as well as chronic sinus pain, the new wave of electricity-based strategies could expand to help people with some of the most widespread chronic diseases in the world, including high blood pressure, arthritis, diabetes, some forms of blindness and even dementia.

For Owens, the new approach has been life-changing. Since Crohn’s is caused by an overactive inflammatory response in the gut, the goal is to inhibit that inflammation by dialing down the electrical impulses zipping between immune cells around the intestines so that the inflammatory

response dies down and aggravated tissue can start to heal. Two weeks after she received the implant in her chest, doctors turned it on to a frequency customized to stimulate a specific nerve at just the right energy level to keep her immune system under control. That evening, she forgot to take her pain medication because she didn't need it. She was able to live pain-free for the first time in decades.

Such promise is already attracting scores of startups and major drug companies. Financial analysts expect the market to reach $7 billion by 2025, and companies like Abbott already have neuromodulation devices approved by the Food and Drug Administration for treating chronic pain. Electroceuticals "are the next wave of new treatments we will have to treat disease," says Kris Famm, PhD, president of Galvani Bioelectronics, a biotech collaboration between GSK and Google's Verily that is focused on developing electricity-based therapies.



The old-school pacemaker is being replaced by tinier versions without leads, which can slip.

FINE-TUNING MESSAGES

It turns out that many cellular functions are regulated by electrical signals that pass through nerves between the brain and the organs where the cells are located. The frequency of those currents determines how active the cells are in performing their assigned function.

Medicine's attempts to exploit this system have grown more refined with time. In recent decades, more effective bioelectronic devices focused on refined modulation of electrical signals—including pacemakers for the heart, cochlear implants, as well as devices to control urinary incontinence and strategies for helping paralyzed muscles to move—have made it to market.

Research is fueling a surge in more sophisticated bioelectronic devices that is delving deeper into complicated neural networks. Innovations in engineering that are packing chips and other components into tinier and tinier kits to implant in the body, with more power to communicate, charge, stimulate and record, are also expanding the range of diseases that might be treated with a bioelectronic therapy.

In the not-too-distant future, scientists anticipate that patients with high blood pressure could get an electrical device that would control how well the kidneys filter fluids, alleviating the need for medication. Or someone with diabetes could avoid the constant cycle of blood checks and pills or insulin shots with an electroceutical device at the pancreas that protects their insulin-producing cells. At Massachusetts General Hospital in Boston, researchers are working on ways to activate nerves in the eye to restore vision in people with retinal disease, while scientists at Johns Hopkins in Baltimore are convinced that manipulating electrical signals in the brain could address conditions from depression to dementia.

Earlier this year, two patients with rheumatoid arthritis had splenic neuromodulation systems, made by Galvani, implanted. The device stimulates the splenic nerve in order reprogram pro-inflammatory immune cells in the spleen to anti-inflammatory cells. Those cells can then migrate to joints, for example. The study will be ongoing for many years, says Famm, so there's no word yet on any changes.

"We expect that this therapy can help patients suffering from a wide range of immune-mediated inflammatory disorders, offering a new approach to get more patients to gain treatment benefits and get closer to disease remission, but we need to conduct additional clinical trials to understand whether and to what degree this will be," says Famm.

"The nervous system really uses electricity as its language," says Robert Kirsch, PhD, chair of biomedical engineering at Case Western Reserve University and executive director of the Cleveland FES (Functional electrical stimulation) Center. "So

electrical stimulation can be used theoretically just about anywhere in the nervous system. We need to learn how to speak that language."

CAPTURING THE SPARK

For now, researchers are beginning that decoding project with well-defined nerve systems. SetPoint Medical, which conducted Owens' trial, is focusing on the vagus nerve, the longest nerve in the body. It's rooted in the brain stem and branches into the neck, chest and abdomen, controlling everything from sensory functions to swallowing, digestion, respiration and heart rate. It serves as a volume control for the nervous system. But researchers are treading carefully to ensure they trace the vagus' myriad fringelike connections to the right tissue and the right function. "It's like trying to make a telephone call by putting the call over every single line that is available," says Kirsch. "It goes to the right line, but it goes to all the other places, too."

So scientists are working on a better road map, building a detailed picture of the major nerve networks in the body. The project, called SPARC (Stimulating Peripheral Activity to Relieve Conditions), is funded by the National Institutes of Health and aims to map out every nerve of the human nervous system outside the brain. That could illuminate new ways to manipulate electrical signals to control cells connected to those nerves. Researchers at universities across the country are assigned different major organ systems, and the resulting nerve map will be available to any scientist interested in finding ways to tap into those neural networks to develop a potential electroceutical treatment.

In order to control signals in the right nerves near the organ in question with the right patterns, a device needs to be small enough to be implanted and interface with the target nerve, remain there safely for decades and be powerful enough to modulate the flood of electrical chatter occurring along that neural circuit. It also needs to communicate with external devices that control the therapy. At Galvani, Famm's team has spent the past six years designing, building and testing such a system. "The next decade is about bringing this to bear broadly as transformational treatments for patients," says Famm.

A REPRIEVE—AND HEALING

For patients like Owens, the early results have been transformative, and she hopes her experience as one of the first to test her device changes the way diseases like hers are treated. Now in her fifth year of clinical remission, she turns on the regulator in her chest for only five minutes in the morning and five minutes before bed. She's back to work as a bioelectronic medicine education and outreach consultant at the Feinstein Institute, helping patients like her learn more about new therapies for treating their autoimmune diseases. What's more, her last colonoscopy showed that half of the damaged tissue in her colon had healed; without the constant barrage from the immune system, her gut is functioning the way it should. "Now my body just works; it just does what it's supposed to do," Owens says. "That's still mind-blowing for me."
—*Updated excerpt from* TIME, *Oct. 24, 2019*

Alice Park is a staff writer at TIME.

On the Hunt

TRACKING INFLAMMATION IN THE TISSUES MAY MAKE IT EASIER TO TREAT AUTOIMMUNE CONDITIONS.

Bioelectronic medicine offers exciting potential, but researchers are exploring other ways to crack the code of complex autoimmune conditions. "We have come a long way in the last 20 years in terms of understanding inflammatory mediators and the cells that are affected in autoimmune diseases, but a lot of our treatment decisions are still dictated by non-patient-specific protocols," explains Dr. Joanne Michelle Kahlenberg, an associate professor of internal medicine at the University of Michigan Medical School. "We're on the verge of developing personalized medicine in autoimmunity. That's where the next 10 years will take us."

As part of the Accelerating Medicines Partnership, scientists across the U.S. are studying cells in the tissues of different organs in an effort to detect inflammation. "The tissue itself may be a better source for looking at inflammatory markers," says Kahlenberg. "We're discovering how to easily sample and study tissue and how that will change our biomarker detection ability. We're hopeful that will lead to more personalized treatments." —*Janet Lee*



Artificial intelligence use in health care almost tripled between 2019 to 2021, according to a Grand View Research analysis.

HIGH-TECH MEDICINE

How AI Is Reshaping Health Care

Artificial intelligence will increase accuracy, decrease diagnosis times and—maybe—improve the doctor-patient relationship.

by Karen Asp

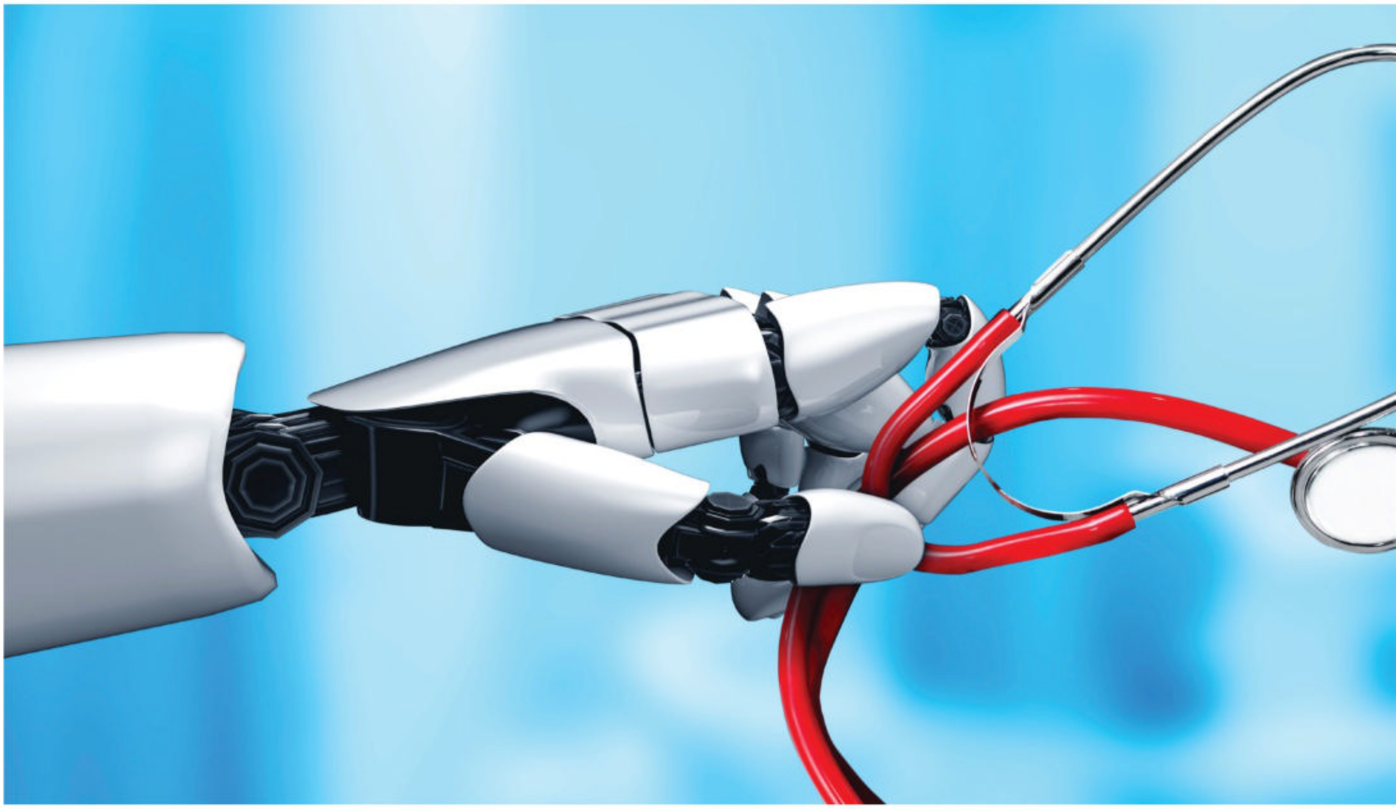


Scanning a pathology report for cancer findings in a quarter of a second may not sound like a huge advance—until you compare it with the average time it takes a human to read such a report: 90 seconds to three minutes. That speedy reading was courtesy of artificial intelligence (AI) technology from Azra AI. Over a three-month period, the tech saved 11,141 hours of manual work—1,392 eight-hour days—according to results published in the *Journal of Clinical Oncology*. Plus, it cut patients' time to treatment by seven days.

This is just one example of how AI is revolutionizing medicine and health care, and experts predict that it will have an even more monumental impact—although not without challenges—in the upcoming years.

THE BRAIN INSIDE

AI might sound complicated at first, especially if you're not tech savvy, but if you've ever called up Siri on your iPhone, used a robot vacuum or asked Alexa a question, you're already familiar with AI. But what exactly is it? "The



textbook definition is an intelligent agent able to achieve a goal defined by humans," says Lurong Pan, PhD, founder and CEO of Ainnocence, a global biotech startup that's accelerating new drug development by using an AI-powered drug-design platform. "At a minimum, AI is an expert system that can replace a certain level of experts' work," Pan says. "At the advanced end, AI is able to achieve scientific breakthroughs beyond what experts or scientists are capable of."

To accomplish this, AI technology undergoes a learning process that's similar to the human learning experience. "Children learn through explanation and repetition, and computers learn in a similar manner," says Connor Landgraf, CEO and co-founder of Eko, which created the first AI-powered stethoscope.

Eko, for instance, feeds its AI machines thousands of heart sounds, distinguishing those that are normal from those that may indicate problems like a heart murmur. With repetition, the computer's algorithm learns to distinguish the heart sounds on its own so the stethoscope can screen for heart disease in 15 seconds. What's more, "it's not only faster but also more accurate than humans," Landgraf says. The AI stethoscope is currently being used by thousands of physicians around the world, even in lower-resource countries, where nurses and other providers can screen patients and share the heart sounds with a remote specialist, thus allowing them the benefit of assessing up to 2,000 people a day.

AI's cognitive abilities, if you will, don't surprise Pan, who says its imagination is massive. "It has a bigger imaginary space than humans," she says, pointing to new drug development where scientists, specifically medicinal chemists, are working to create new small-molecule drugs, which are compounds with low molecular weight. They're typically the kind found in everybody's medicine cabinet and include aspirin and the antihistamine diphenhydramine (Benadryl).

With only humans doing the testing, the chemists have to run roughly 6,000 tests before finding one molecule that can be sent to clinical trials. With AI, however, that gets cut to about 150 tests. "With fewer molecules being tested (which means less cost and time) to reach

ABOVE *Adoption of AI technology is already leading to reductions in job opportunities in certain areas.*



clinical stage, the drugs eventually reach the patient faster and at a cheaper price," Pan adds.

POSITIVE EFFECTS

The health care industry has been embracing AI for at least the past five years and in the case of drug discovery, even longer. "It's possible that the average consumer may not be aware that AI is being used behind the scenes in a whole host of areas," says Chris Cashwell, CEO and founder of Azra AI, whose technology is being used in 200 hospitals in the United States.

The applications for AI may be vast, but according to a study in the *Journal of Family Medicine and Primary Care,* the technology's uses in health care mainly include the following areas: developing drugs, diagnosing disease, analyzing health plans, monitoring health, digital consulting, treating with surgery, managing medical data and personalized medicine.

This doesn't mean, though, that hospitals will one day be filled with robots—although according to a 2020 study of almost 170,000 patients, published in *JAMA Network Open*, 15.1% of all general surgeries were being performed robotically as of 2018. People are still required to oversee AI technology. But AI can help humans be more productive and do their jobs better, a win for the cost-conscious health care system, physicians and most importantly, patients. "One of the most important things AI does is allow clinicians to spend more time with patients and less time with data," Cashwell explains.

A recent study in *JAMA Network Open*, for instance, evaluated whether an AI system could improve physicians' abilities to extract patient information from electronic health records (EHR). Not only did the AI system help maintain a high accuracy, it also cut physicians' review time of patients' records by 20%, a savings that might go toward their patient visits since doctors often review health records before each patient's appointment.

That may not sound dramatic, but researchers say the savings could add up over time with each patient. Along with the potential time savings, "AI-augmented EHR systems could reduce mistakes and even synthesize together disparate information to help doctors," says Ethan A. Chi, the *JAMA* study's co-author and a recent Stanford University graduate. For example, an AI-backed EHR system might point out a possible harmful drug interaction or signal a rare diagnosis that physicians missed.



Only 30% of lung nodules—some of which could be cancerous—are followed up on by the patient.

WHAT THE FUTURE MAY HOLD

Although AI has already had a significant impact on health care and drug development, experts say the future is even more promising. Pan believes AI will have a significant impact on the roughly 10,000 diseases—8,000 of which are rare genetic diseases—that still have no treatment. "With the help of AI, it's possible we can find treatments for these diseases by expediting the diagnostics of them," she says. The hope is to lower the cost and time for drug discovery for each of these diseases by 50 to 80%, which will make treatment more affordable, she adds.

Azra AI's Cashwell agrees. "With more data about individuals and more treatments targeting personal traits, care will become more individualized," he says. In cancer treatment, he notes that Azra is moving toward improving the diagnosis of incidental findings, results found during a test a doctor orders that have nothing to do with the reason the test was ordered (like a nodule on the lung spotted during an abdominal CT scan).

With the help of AI, these cases could be discovered, tracked and monitored more closely. "The goal is to get people the proper care so they don't come back a year later with stage 3 cancer as opposed to a small procedure to remove a nodule," Cashwell says. AI could even help provide better guidelines for knowing when an incidental finding doesn't need to be pursued, potentially reducing overtreatment.

AI-driven products inside the home is another opportunity for innovation, says Eko's Landgraf. "Rather than having heart or lung exams done in a medical office, individuals who have heart or lung disease might someday be able to do this remotely in the same way you use a blood pressure cuff to monitor blood pressure at home," he says.

This doesn't mean AI is without drawbacks. One is that it is mostly data dependent. The problem? "Data quality limits its application scope," Pan says. (In other words, bad data in equals bad data out.)

It's also technology that's not easily explained or trusted, which is concerning for some people. "Most AI is a black box of knowledge that can't be explained by conventional chemistry or biology rules so it's hard to be trusted by experts," Pan says. That may be why, in fact, some health care systems and physicians are reluctant to use AI. It could also be that they're worried about the loss of jobs.

And while its potential is promising, it's also only the beginning. Perhaps only AI can know how it will shape health care in the future.

Karen Asp is an award-winning freelance writer in Fort Wayne, Indiana.

Who's Minding the Robot?

IN THE BACK OF EVERY SCI-FI FAN'S HEAD IS THE FEAR THAT AI COULD BECOME SENTIENT AND TAKE OVER.

Hollywood movies like to depict robots, essentially AI-powered machines, taking over the world. That, of course, begs an obvious question: Could they get smart enough to take over?

The short answer is no, namely because they have data scientists who oversee their every move. "They monitor these machines on a continual basis," says Azra AI's Chris Cashwell, using the analogy of a swimming pool to explain the oversight: In every pool, somebody has to test the water constantly to make sure the water chemistry is correct. That's essentially what data scientists do with AI. They just don't program and go. "They're reaching into the data every week, day or hour and seeing if the machine is processing the data correctly and accurately," he says.

That, by the way, applies to the input, too, as there are specific techniques to check for bias and interference. "This ensures that input is true and hasn't been interfered with in some way," he says.

Yet what happens if the results look fishy? "There are approved and agreed-upon tolerance levels where the results should come in," Cashwell says. "If they fall outside of that, data scientists find out what's going awry and retrain the model and the algorithm before testing it to make sure the problem's been fixed."

At least in health care, AI won't be taking over anytime soon. The robot performing a knee replacement won't suddenly decide it's better to just cut off the leg. It's still the humans behind the program that you have to watch out for.



AI models are able to spot the earliest signs of cancer in the lungs or breast.

FROM THE *TIME* VAULT

The Rise of the Machine

AI is most powerful as a partner for the physician.

By Alice Park

Being newly diagnosed with a heart problem, especially something as ominous as heart failure, is stressful and potentially overwhelming. There are medications—probably several, since most people who are diagnosed with heart failure also have cardiovascular disease and/or high blood pressure. There's follow-up monitoring and recommendations from the doctor about how to eat or exercise. And then there's the fear. *What does that fluttering in my chest mean? What if I forgot to take my pill?*

Patients could call their doctor or go to the emergency room when these questions arise, but it could take hours to get a response and cost thousands of dollars, if not more, to simply be told that it's fine. To save doctors time while still attending to patients' concerns and sussing out red flags for emergent care, researchers have leveraged the power of AI to come up with a personal medical assistant-type device that can provide reminders, answer many common questions and triage potential problems: Mabu, a 15-inch-tall, wide-eyed yellow robot sits on a countertop in the patient's home and interacts with them about their health, prescription drugs and even the weather. "It creates a level of engagement that you can't get through a screen," says Cory Kidd, CEO and co-founder of Catalia Health, Mabu's creator.

Mabu is among the latest examples of what machine learning, or artificial intelligence, can accomplish in medicine. The questions she asks come from a recipe that combines best practices that doctors use to monitor heart failure with data from how physicians interact with patients—the questions they ask as well as how they respond—to isolate and manage not just medical symptoms but psychological barriers like anxiety and depression that often make dealing with chronic diseases difficult. She is also designed to not just spit out the same questions every day, but to change her lineup depending on the patient's answers. If they say they haven't had any problems breathing while doing normal tasks like cooking or walking to the bathroom, for example, Mabu goes on to ask about mood and other activities they may be doing. She's even programmed to make jokes—and to stop making jokes if the patient doesn't respond to them. If a patient complains of shortness of breath, she would ask other questions to determine how serious the symptoms are, and then advise them to contact their doctor or care team.

'WE CAN DECOMPRESS SOME OF THE CLINICAL SIDE OF MEDICINE WITH MACHINES BUT THEY CAN'T REPLACE THE HUMAN TOUCH OF THE DOCTOR.'

—Dr. Eric Topol

Medicine has long seemed ripe for more examples of intelligent robots or computers that can make sense of the reams of data that are the lifeblood of the profession. But its most ballyhooed effort has had a mixed record in the clinic: After IBM Watson successfully mastered the game show *Jeopardy!* in 2001, IBM partnered with Memorial Sloan Kettering Cancer Center to create an algorithm for improving the diagnosis and treatment of various cancers. The program, Watson for Oncology, was introduced at a number of hospitals around the world, but in 2016, MD Anderson Cancer Center decided to put its partnership on hold. A stumbling block for the hospital, according to reports from its former executives, involved challenges in pulling relevant patient information from electronic health records. And some doctors that used Watson felt IBM's decision to train Watson for Oncology with experts at a single institution led to biases in the treatments it recommended. IBM says it's been transparent about its training strategy, and no patients were harmed due to Watson's advice. The company continues to work with other health

care organizations and hospitals. (IBM Watson Health is now known as Merative.) Officials at MD Anderson and Memorial Sloan Kettering declined to comment on their IBM Watson projects.

TRYING TO KEEP IT (RELATIVELY) SIMPLE

Looking back, many experts agree that the spotty record of early applications of AI don't necessarily signal the demise of machine learning in medicine. Instead, they highlight the need to be humble with any innovation, especially one that comes with too much hype. "IBM was too ambitious in my opinion," says Steve Jiang, PhD, director of the medical AI and automation lab at UT Southwestern.

Today's efforts in AI are somewhat less flashy, though still potentially revolutionary, and all seem to recognize one vital lesson: Treating patients is both art and science. Rather than attempting to replace physicians in medical practice, experts say that AI can, and should, become a valuable tool in enhancing what doctors do.

The medical world is still figuring out how best to do this, researching the use of AI in everything from boosting IVF success rates to predicting the development of foot ulcers in diabetic patients to improving blood-glucose tracking. Machines are best at digesting massive amounts of data and picking out patterns or seeing things that human brains can't—commonalities and differences that could translate into factors that might mean a higher risk of cancer, say, or the earliest signs of depression. But only a few fields are currently collecting information in a standardized, quantifiable way that machines can immediately exploit. Most medical information, even in electronic health records, isn't documented in consistent and discrete ways that can be easily extracted by a computer. And what machines can't do is factor in intangible and unquantifiable things that doctors intuitively get from knowing their patients for years or from being able to look them in the eye and sense when they're not being completely truthful.



Robotic surgeries aren't necessarily faster or more accurate than traditional techniques—yet.

"We need to let the machine do what it does well—such as ingesting a whole lot of scientific papers and organizing them—and let the clinician make the final decision on what should be done to treat a particular patient," says Kidd.

There is progress toward that goal. Among the most promising applications of AI are as stand-ins for doctors who can't see patients face-to-face as often as they ideally would, and in laboratory analysis that is more accurate than what human doctors can do on their own. In both cases, man and machine must work together.

Robots like Mabu, for instance, bridge the gap between doctor and computer, obtaining vital information from patients who require frequent check-ins and transmitting it to the professionals who can then tailor medical care accordingly. Armed with vast knowledge about what symptoms serve as red flags for heart failure, and which questions can best ferret out those symptoms, Mabu is acting similarly to how a doctor would—but without the hassle of appointments.

FORMING A PARTNERSHIP

It's becoming increasingly clear that patients won't be talking to computer screens for all of their health needs. Instead, believes Dr. Eric Topol, director and founder of the Scripps Research Translational Institute, and author of *Deep Medicine: How Artificial Intelligence Can Make Healthcare Human Again*, AI will act as a partner, freeing doctors to concentrate more on the art of medicine that machines aren't likely to master. "So many things in medicine need context and the human touch. Nobody wants to get a diagnosis like cancer or serious heart disease through a chatbot." *—Updated excerpt from* TIME, *March 21, 2019*

FROM THE *TIME* VAULT

Bringing Humanity Back to Medicine

ONE EXPERT REVEALS HOW TECHNOLOGY MIGHT BE THE ANSWER AFTER ALL.

Dr. Eric Topol has always been fascinated by the doctor-patient relationship. In his 2016 book *The Patient Will See You Now*, he explored how patients have more power and insight over their health than ever before, thanks to smartphones. In his 2019 book, *Deep Medicine*, he delves into the erosion of the doctor-patient relationship and how artificial intelligence may actually help instead of hinder it. *TIME* asked him to weigh in on whether AI is taking us down an impersonal path.



Cardiologist Eric Topol parses new research on Twitter.

How do we re-establish a beneficial doctor-patient relationship?
The answer came when I started a deep dive into artificial intelligence. It dawned on me that using technology to enhance humanity is the ultimate objective here. It's counterintuitive. But for doctors, what this means is the ability to have all of the data about a person assimilated and analyzed, to have scans and slides read. That liberates doctors from keyboards so they can look patients in the eye.

People can track their health now with their smartphones. Is that a good thing?
Some of that data will be enlightening, and really helpful. But some of it is going to be terrible noise and even lead to unnecessary testing and anxiety. It's a mixed bag. But we've seen citizen empowerment across all other sectors, and while health care is trailing, it is going to continue to get a lot of momentum.

What are the best examples of how AI can work in medicine?
We're seeing rapid uptake of algorithms that make radiologists more accurate. The other group already deriving benefit is ophthalmologists. Diabetic retinopathy, which is a terribly underdiagnosed cause of blindness and a complication of diabetes, is now diagnosed by a machine with an algorithm that is approved by the Food and Drug Administration. And we're seeing AI hit at the consumer level with a smartwatch app with a deep learning algorithm to detect atrial fibrillation.

Is that really artificial intelligence, in the sense that the machine has learned about medicine like doctors?
Artificial intelligence is different from human intelligence. It's really about using machines with software and algorithms to ingest data and come up with the answer, whether that data is what someone says in speech, or reading patterns and classifying or triaging things.

What worries you the most about AI in medicine?
I have lots of worries. First, there's the issue of privacy and security of the data. And I'm worried about whether the AI algorithms are always proved out with real patients. Finally, I'm worried about how AI might worsen some inequities. Algorithms are not biased, but the data we put into those algorithms, because they are chosen by humans, often are. But I don't think these are insoluble problems. *—Excerpted from* TIME*, March 14, 2019*



‘GENOMICS IS PART OF A DATA EXPLOSION. THE KEY IS FIGURING OUT WHAT DATA TO GIVE TO THE DOCTOR OR PATIENT AND WHEN.’

—Dr. Peter Hulick

The Promise of Precision Medicine

Mapping the human genome is easier than ever. Putting that data to use—for the benefit of patients—is the hard part.

By Karla Walsh

Once scientists spot an errant order of genes, it may be possible to snip out the problematic sequence. *For more on that, turn to page 38.*

Just like one set of sneakers doesn't fit all feet, no one diet is ideal for every individual. Some people can't process milk proteins, while others experience allergic reactions to proteins in wheat. And as much as the diet trend du jour leads Americans to believe there's one "right" way to eat, an individual's ideal diet differs a remarkable amount based on genetics, biology, gut microbiome, medical history, body composition, exercise and their environment.

So imagine a future in which, instead of being told to just eat a healthy diet, people work with both their doctor and a nutritionist to find a tailored eating style that matches their specific genetic predispositions and gut microbiome. Instead of limiting calories, your ideal diet plan could revolve around adding more specific vitamins, minerals, macronutrients and certain foods that jive with your DNA and help reduce the risk for diseases that run in your family.

"Precision nutrition aims to take into account everything about a person—their genetics, environmental exposures and health behaviors—then design a way to prevent and treat illness that is ideally optimized for that specific person. It's the opposite of 'one size fits all,'" says Dr. Francis S. Collins, the former director of the National Institutes of Health.

Medicine is nowhere near being there yet and the timeline for this level of nutritional specificity becoming a reality is tough to predict. That's because scientists don't yet have enough data (data being mapped genomes from individuals) to be able to spot commonalities among DNA of healthy individuals versus those with a specific condition. That said, the future could come much sooner than one might guess.



MAKING IT PERSONAL

Precision nutrition is just a small aspect in the larger arena of precision medicine (also known as personalized medicine), an emerging field that considers individual variability in genes, environment and lifestyle to pinpoint specific risks for health conditions and to treat those health problems in a more tailored, less general way. There are currently more than 2,000 active research projects involving precision medicine, ranging from the demographics and risk factors associated with inflammatory skin diseases to genetic variants that might contribute to gender identities, to depression among people with diabetes. "Precision medicine is personalizing care for an individual, using data specifically about the person," explains Dr. Josh Denny, chief executive officer of the government-funded All of Us Research Program based in Bethesda, Maryland.

Treatment and prevention for everything from blood clots to heart attacks to seizures have been improved based on personalized medicine, and the field is also impacting the cancer landscape. Whether in the breast, brain, lung, blood or liver, every cancer has a unique set of DNA changes that causes otherwise normal cells to "grow out of control," Collins says. "Knowing the specific genes and pathways that are driving the cancer in an individual can provide a much better chance to pick the best therapy. This is called 'precision oncology,' and is rapidly becoming the standard of care."

Doctors are also using precision medicine to better and more safely prescribe drugs, instead of resorting to the trial-and-error method—a field called pharmacogenomics. "Just as our genes determine our hair and eye color, they also can affect how our bodies respond to medicine. Most

medications are processed by the body, but some variants in genes can affect the breakdown of the drug or its elimination from the body," explains Denny. "If that happens, you can end up with too much or too little of the drug in the bloodstream, leading to lack of efficacy or side effects."

In March 2015, then-President Barack Obama tapped the National Institutes of Health (with $215 million in funding) to launch the nationwide All of Us program. The goal: Build a health database with genomic information from 1 million people by 2026 to pinpoint risk factors for certain diseases, determine which treatments work best for individuals of different backgrounds and connect people with clinical studies that can make their lives healthier and longer. All of Us is a "taxpayer-supported research program that aims to speed medical breakthroughs on a wide range of diseases for public benefit, not commercial goals," Denny says. It's one of many current projects that are attempting to progress the field of personalized medicine.

There are also a number of universities that have set up DNA biobanks and another NIH initiative through the National Heart, Lung and Blood Institute called Trans-Omics for Precision Medicine (TOPMed) Program, which is focused on research related to heart, lung, blood and related sleep disorders. All sources work corroboratively to share knowledge, Denny says.



Handling participants' DNA results poses challenges for doctors and insurers as well as patients.

DOWNSIDES OF A PERSONALIZED APPROACH

To tap into the full potential of precision medicine, "we need to really understand what causes disease, and how the individual variations in our lifestyles, DNA and exposures to potential disease triggers affect our health," Denny says. "That's why it's important to increase participant data so that the information we have is more inclusive of populations who have historically been left out of research."

With personalized medicine, preventative interventions and treatments are more likely to work because they are optimized for that patient. But the study results are just starting to come in, so doctors using personalized medicine still feel like they're walking on unsteady ground.

One major barrier to getting enough DNA in the database is cost. While it's more affordable to map genes (see "Gene Sequencing, Decoded," opposite page) via saliva or blood tests, it's still not cheap. In mid-2015, the cost for a full high-quality map of a human genome clocked in at more than $4,000. By late 2015, that had fallen to about $1,500. Today, the National Human Genome Research Institute estimates an average whole genome sequence (which includes about 3 billion base pairs) costs a little less than $1,000. Multiply that by a million participants required for the All of Us project and it's a billion-dollar price tag that's currently being funded by tax dollars. But proponents of precision medicine say the payoff is a reduction in unnecessary testing and prescription drugs. It will also allow for the development of more affordable treatment options and perhaps prevent painful and costly diseases before they happen.

Another plus is that it will eventually provide more equitable health care. Traditionally, medical research has mainly included people of European ancestry. Especially with precision medicine, those who aren't included in the genome collection can't fairly reap the benefits of research advances. All of Us, for one, has made diversity a priority. So far, about 50% of participants are nonwhite, and more than 80% are diverse in gender, sexual orientation, socioeconomic status, education, disability and health status, Denny confirms.

And while it is still pricey, genomic sequencing is becoming a surprisingly fast process. As of January 2022, scientists at Stanford Medicine have developed a gene sequencing process that can tackle the task in an average of eight hours per person. But that's just the beginning. From the genomic data, experts need to devise treatment plans, medication and more, which involves clinical trials and other research. It's a seemingly monumental undertaking. The evolving nature of personalized medicine will allow researchers and doctors to tap into a robust hub of information, but it will take time for scientists to investigate the data and translate research findings into clinical care, Denny notes.

Of course, in an era of data breaches and privacy concerns, many people are justifiably concerned about sharing their most personal, unique data. To help ease these worries, experts confirm that any personal details will be "decoupled" from the genome itself before being stored in a secure cloud-based virtual platform, and the biosamples for All of Us participants are warehoused in a private facility at the Mayo Clinic. Any personalized medicine research that's conducted on the samples must comply with the White House's data security policy principles.

THE PAYOFF

"Participants can choose to learn more about their genetic ancestry and traits, and we will begin returning health-related genetic information to participants this winter," Denny says, referring to the data All of Us participants will be receiving. "We are able to provide robust health-related information on genetic diseases because we perform whole genome sequencing. Genetic health counselors will be available to explain the results if necessary," he says. (Detractors argue, however, there aren't enough genetic counselors available to explain what DNA results really mean.)

"The challenge we're facing with genomics data," says Dr. Peter Hulick, director of the Mark R. Neaman Center for Personalized Medicine at NorthShore University HealthSystem in Chicago, "is organizing it in such a way that the right amount of data, at the right time, is presented to the physician or patient so they can take the best next step for their health."

Karla Walsh covers health and food from Des Moines, Iowa.

Gene Sequencing, Decoded

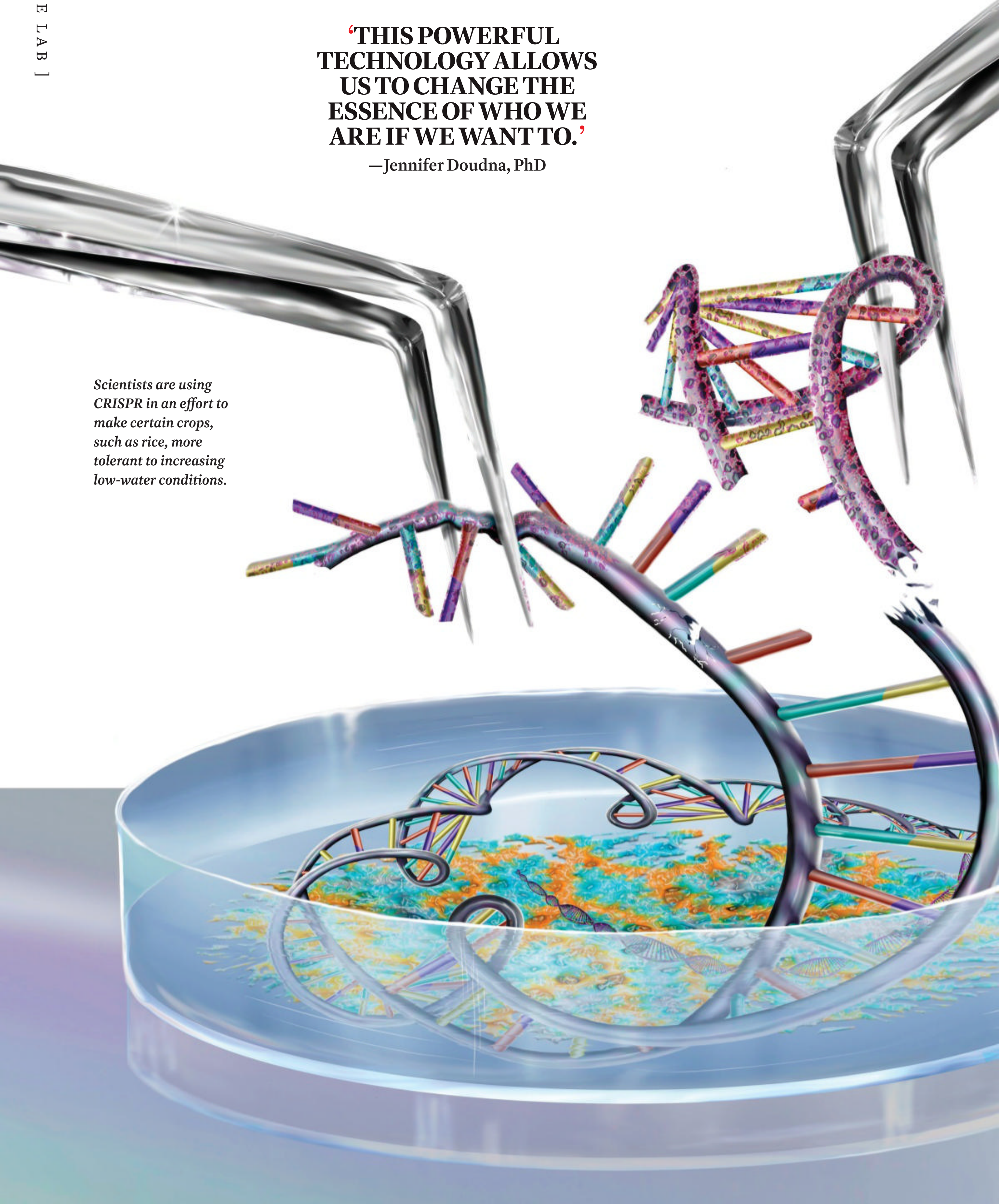
TRACKING THE ORDER OF LETTERS IS EASY.
THE IMPLICATIONS OF THAT ORDER ARE MORE CHALLENGING.

Think of DNA (short for deoxyribonucleic acid) as a blueprint that explains how to build a body. One person's genome is a collection of all of their genes, which are made up of DNA. "Two unrelated individuals share 99.9% of their genomes, but that still leaves enough variations to account for a huge amount of human diversity," says Dr. Francis S. Collins.

Since humans are such complex creatures, that 0.1% offers enough opportunity for variations that impact susceptibility to conditions like diabetes, cancer and Alzheimer's disease. To identify those risk variants for common conditions, researchers study the location of base pairs within DNA of people affected with a condition and then compare it to those who are not.

Using a blood or saliva sample treated with a gel, scientists scan the DNA into a computer. There, they can trim pieces of DNA into readable "bites" of about 600 base pairs and add DNA tags that act like barcodes on an item in the supermarket to each base pair letter—A (adenine), C (cytosine), T (thymine), G (guanine). Then they compare one individual's results to the larger pool of genomes to see where these "barcodes" might appear out of usual order.

"When they find DNA 'spelling' that appears more frequently in affected persons, they have mapped a gene that contributes to that illness," Collins explains.



'THIS POWERFUL TECHNOLOGY ALLOWS US TO CHANGE THE ESSENCE OF WHO WE ARE IF WE WANT TO.'

—Jennifer Doudna, PhD

Scientists are using CRISPR in an effort to make certain crops, such as rice, more tolerant to increasing low-water conditions.



FROM THE *TIME* VAULT

CRISPR Celebrates 10 Years

The gene-editing technology can help eradicate diseases and address pressing agricultural and climate issues.

By Alice Park

Jennifer Doudna, PhD, was staring at a computer screen filled with a string of As, Cs, Ts, and Gs—the letters that make up human DNA—and witnessing a debilitating genetic disease being cured right before her eyes. Just a year earlier, in 2012, she and microbiologist Emmanuelle Charpentier, PhD, had published a landmark paper describing CRISPR-Cas9, a molecular version of autocorrect for DNA, and she was seeing one of the first demonstrations of CRISPR's (clustered regularly interspaced short palindromic repeats) power to cure a human disease. She was in the lab of Dr. Kiran Musunuru, a Harvard researcher who was eager to show her the results from an experiment he had just finished using CRISPR to splice out a single aberrant letter from the 3 billion base pairs of DNA in a sickle cell anemia patient's cells. With the mutated letter gone, the cells would, presumably, start forming healthy red blood cells that carry oxygen instead of the harmful versions that make the disease so painful for the 100,000 people living with it in the U.S. Post-CRISPR, the mutation responsible for causing the patient's sickle cell anemia was no longer detectable.

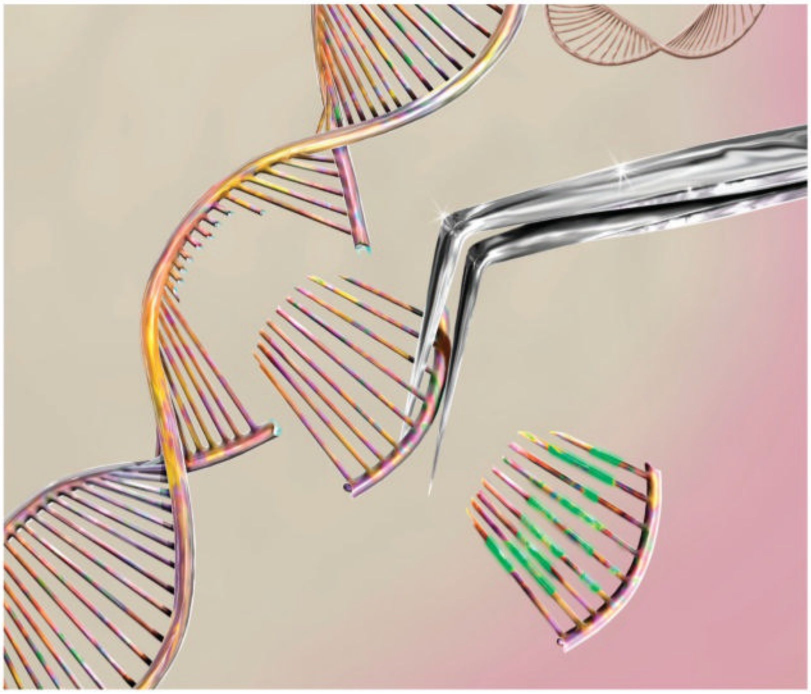
The technology that Doudna, a professor in chemistry and molecular and cell biology at the University of California, Berkeley, and Charpentier, who was then at the University of Vienna, first described in a paper published 10 years ago was breathtaking in both its power and simplicity. When opportunistic viruses insert their genetic material into bacterial genomes, using their hosts to churn out more copies of themselves, the bacteria respond with their own genetic defense: They generate repeated DNA sequences that sandwich the viral genes and provide instructions for powerful enzymes that can splice out the intruding DNA.

The duo's teams worked out a way to apply the same strategy to targeting and snipping out specific portions of DNA in the human genome—namely those containing mutations responsible for genetic disorders like sickle cell anemia. CRISPR is programmed to edit DNA only at certain places, operating like a pair of molecular scissors equipped with enzymes that can cut the DNA, and a genetic GPS guide made up of another complementary genetic material called RNA that can find the designated DNA sequence.

In the years since their research was published, Doudna and Charpentier won the 2020 Nobel Prize in chemistry and CRISPR has driven innovative thinking in nearly every aspect of life. Scientists and companies are testing CRISPR not just to treat human disease, but also to improve plant crops and alter the populations of microbes in livestock that contribute to greenhouse gasses, due to their methane emissions, and ultimately to climate change. Drought and pesticide resistance, more carbon-friendly livestock and lower-emission populations of gut microbes are all possible with CRISPR.

As with any cutting-edge technology, the power to edit genomes also has a dark side. While it holds promise for curing intractable genetic diseases, it could potentially also be used to impart certain traits, like eye color, hair color, intelligence or specific physical attributes, which could then be passed on to future generations. Potential applications to cells like eggs, sperm, and embryos—where the changes can be inherited—keep Doudna up at night.

Over the past decade, dozens of companies have emerged to take advantage of CRISPR to treat human disease, and Doudna's nagging fear about CRISPR even came true: In 2018, a scientist in China used the technology to permanently alter the genomes of twin girls to be resistant to HIV (their father was HIV positive), despite Doudna and other leading scientists around the world having agreed to a moratorium on using CRISPR on embryos. (The scientist was jailed for violating medical regulations with his unorthodox experiment.)



Research using CRISPR has spurred patent disputes among university powerhouses.

"I am always a little bit worried as more and more companies jump on the CRISPR bandwagon and start clinical trials," she says. "What if those trials get ahead of themselves, and a negative event occurs that sets the whole field back?"

If the first 10 years of living with CRISPR were about working out the scientific challenges behind editing genomes, the next several decades will be about coming to terms with the technology's revolutionary power.

WHERE WE GO NEXT

The Innovative Genomics Institute (IGI) at Berkeley is Doudna's answer to the profound questions raised by the gene-editing technology she introduced to the world. "I quickly realized very early on that there was so much to do that there was no way my academic lab could tackle it," she says. "We would have to involve a much bigger team." The Institute convenes experts from virology, genetics, clinical medicine, agriculture and climate—all focused on finding the most responsible ways to transfer CRISPR into the real world.

The first forays into treating human diseases with CRISPR have focused on conditions like blood cancers, in which doctors can remove cells from patients' bone marrow, which produces immune and blood cells; edit them with CRISPR to remove unwanted mutations; and then return the "fixed," healthy cells back to the patient. Other research is using a similar strategy to treat sickle cell anemia and a variety of cancers, including non-Hodgkin's lymphoma.

Scientists, including Doudna's group, are continuing to refine the technology by finding ways to edit even more precisely. While CRISPR is effective, it's not perfect at "making the type of change that you want to make at the desired position," Doudna explains. Making it so is critical as CRISPR expands into trying to treat more complex conditions, like dementia and heart disease, that are the result of multiple changes in a variety of genes.

One of Doudna's former students, Ben Oakes, co-founded Scribe Therapeutics with her, and their team has pioneered a CRISPR system relying on a different enzyme, or DNA-cutting molecule, than the original CRISPR platform. In animal models of Lou Gehrig's disease (ALS), the system seems to edit the targeted mutations more efficiently and contribute to a longer lifespan for the animals than the original CRISPR platform.

That will hopefully be the case in people as well, as more scientists find ways to use CRISPR directly inside patients' bodies. In 2014, Doudna co-founded Intellia Therapeutics, and its scientists have tested a CRISPR-based intravenous treatment for transthyretin amyloidosis, a relatively rare disease involving the buildup of an abnormal form of a protein in the body, causing damage to the heart and nervous system. The treatment, tested in a small number of patients, successfully edited the target genes in the liver and led to up to a 93% drop in blood levels of the abnormal protein a month after the infusion, the company reported in June. It's the first demonstration of the safety and efficacy of CRISPR-based editing in a patient's body, and "how to take something that is incredibly powerful in the test tube or petri dish and make it start to behave like medicine," says Intellia president and CEO Dr. John Leonard.

THE POWERFUL FUTURE OF GENE EDITING

CRISPR is making us rethink certain diseases and how it may be possible to cure them versus manage or treat them for a lifetime. The dialogue about climate change has also been redirected, given the possibility that CRISPR could help address major sources of organic carbon emissions at their source, in the gut microbiomes of animals.

There is no turning back the clock on the incredible scientific sovereignty that humans now have over their world, and Doudna is keenly aware of her responsibility in making sure that power is wielded through thoughtful collaboration. She is talking with the U.S. Food and Drug Administration about CRISPR-based therapies for human diseases that appear to be coming fast and is reassured that the agency is trying to stay ahead of the thorny questions editing the human genome will pose. However, while Doudna is optimistic that the transparency and open dialogue that she has advocated for the past 10 years about CRISPR will push the technology in the right direction, she is also aware that it will be impossible to completely control CRISPR as science moves forward. "I'm not a hyperbolic person, but I'm trying to alert people to the fact that this is really going to change things."

—Excerpted from TIME, *July 1, 2022*

Using CRISPR to Track COVID-19 Variants

THE TECHNOLOGY HAS PLAYED AN IMPORTANT ROLE DURING THE PANDEMIC.

When Jennifer Doudna's lab researchers were desperate to continue their time-sensitive work during the lockdowns in 2020, part of her team at the Innovative Genomics Institute developed a diagnostic COVID-19 test for all of Berkeley's staff, students and faculty in just three months. By September 2020, the lab was federally certified to provide diagnostic tests and began testing frontline workers and underserved communities in the Bay Area.

Using CRISPR-based strategies to identify pathogens, the Innovative Genomics Institute's scientists were able to quickly detect new variants by picking out changes in SARS-CoV-2's genetic sequences, and in May the lab launched a new assay that can detect which variant of the virus patients are infected with. The pandemic provided an opportunity for CRISPR to flex its muscles as a tool for potentially tracking and detecting new infectious disease culprits, as well as variants. Such surveillance would allow public-health experts to better predict where and when to dedicate additional testing and treatment resources.





[SECTION 2]

THE DOCTOR IS IN

Despite the pandemic slowdown, medical knowledge is advancing at an exponential pace.

Breakthroughs in magnetic resonance imaging (MRI) technology, including the use of artificial intelligence, are improving its quality and diagnostic ability.



Treatment vaccines, which aim to trigger the immune system to fight an existing cancer, are different from vaccines that are used to prevent the cancers that are caused by viruses.

Making Inroads Against Cancer

Groundbreaking new treatments mean improved outcomes for patients, and experts believe that advancements will only get better as time goes on.

By Karen Asp

Cancer is the second leading cause of death in the United States, and while the public may be holding out hope that every last case of it will someday be curable, that magical thinking has long been abandoned by researchers. "While some cancers are curable, scientists never talk about curing cancer because we know it can come back," says Mona S. Jhaveri, PhD, a cancer researcher and founder and director of Music Beats Cancer, a crowdfunding platform that addresses critical funding gaps for cancer-fighting innovations and research. "This disease involves genetic changes, and as you hit cancer from one direction, it can work around your treatment strategies."

That's why researchers have been devoting massive amounts of time and energy to developing new treatment therapies. Certainly, traditional approaches like surgery, chemotherapy and radiation remain a vital part of cancer treatments, but visionary new therapies mean that cancers can be treated more effectively, offering new hope to people who are diagnosed with the disease.

GOOD NEWS AND BAD NEWS

It's fair to say that decades ago, a cancer diagnosis was considered a death sentence. Even as recently as 1991, 215 people out of 100,000 were dying from cancer every day. Fast-forward to 2019 and that number dropped to 146 per 100,000, according to the American Cancer Society. Lung, colorectal, breast and prostate cancers—four of the most common types in the United States—have seen the most significant improvements in survival. Today, almost half of all cancer patients can expect to live five or more years after their diagnosis, per the National Cancer Institute.

While much of this success can be credited to advances in screenings and early detection, improved treatment is also playing a role. "Of all of the cancers in the world, 80% of them are solid tumors, and for decades, all we did was cut them out, treat them with radiation or poison them with chemotherapy," says Dr. Michael Zinner, a cancer researcher and chief executive officer and executive medical director of Miami Cancer Institute, part of Baptist Health South Florida. "Then came along targeted therapies, which have made all of the difference, the analogy being that we're no longer doing carpet-bombing and killing everything. Instead, we're using laser-targeted missiles to hit specific parts of the cancer and kill it, but not the cells around it."

In spite of improved outcomes, though, the reality is that cancer diagnoses continue to rise. "Cancer is not a disease on the decline," Jhaveri says, adding that rare cancers like pancreatic, thyroid, and head and neck are becoming more common, as are breast and colon cancers in younger patients. "More people are being diagnosed with cancer each year."

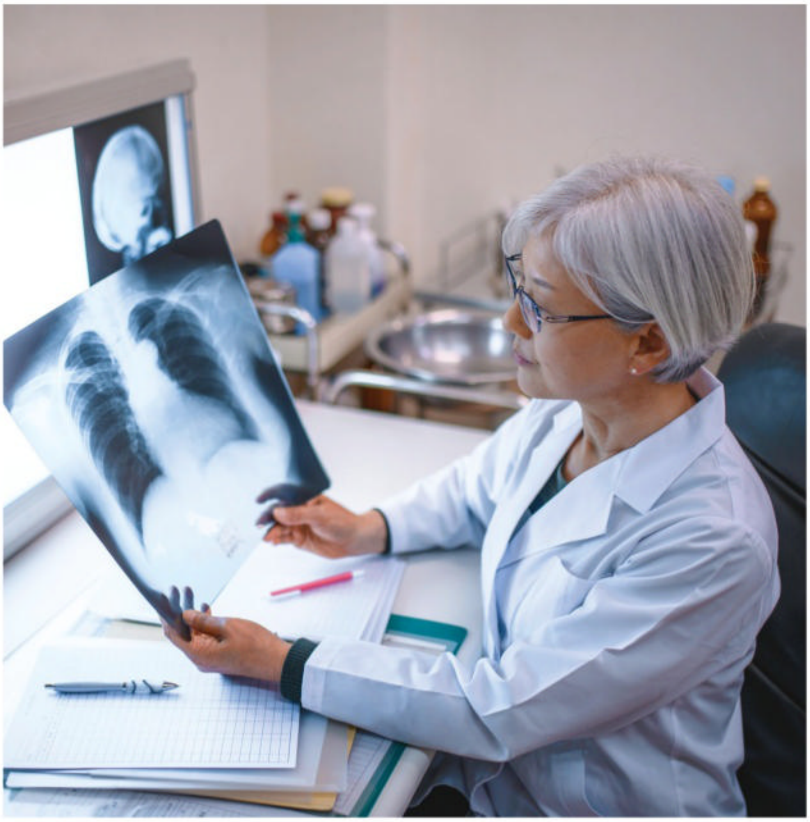
Even more worrisome, because of a lag in cancer screenings during the pandemic, patients are showing up with more advanced diagnoses. "Reports are coming out from radiation therapists who are seeing more advanced disease then they did in 2019," Zinner says. "Will it make a difference in terms of survival? We don't know, but probably yes."

GETTING PERSONAL

More cancer-treatment options are available than ever. There are seven main types of treatments, according to the American Cancer Society, with two of these—targeted therapies and immunotherapies— having the most

significant recent advancements. "There are some, like kidney cancer, that we had no treatment options for 20 years ago, but these new treatments have changed the lives of people with these cancers," says Dr. William L. Dahut, chief scientific officer with the American Cancer Society.

Targeted therapies use drugs like monoclonal antibodies and small-molecule drugs to identify and attack cancer cells without harming the body's normal cells. In the past, all people with a certain type of cancer, such as lung cancer, were treated pretty much the same. No more. "Over time, we've learned that there are multiple different subsets of lung cancer (and other cancers) which respond to very targeted therapy based on mutations in the cancer itself," Dahut says. "These drugs are designed to treat what we call driver mutations, which lead to the progression of cancer, as well as new mutations that often develop in individuals." Lung and kidney cancers and melanoma are examples of cancers responding well to targeted therapy.



A simple chest X-ray can reveal a lung cancer, but it's not a reliable screening tool. A computed tomography (CT) scan is more accurate.

Meanwhile, immunotherapy activates a patient's own immune system to attack cancer. The immune system is designed to spot foreign invaders like viruses and bacteria and mount an attack against them. Yet in individuals with cancer, the immune system is no longer able to recognize this threat (see one way to get around this in "Checkmate for One Disease?" on page 48). Through immunotherapy, though, the immune system can be turned back on and directed to kill cancer cells, Zinner says.

Although the concept has been around for centuries, the first immunotherapy for cancer was only approved in 2011. "For a long time, researchers thought the immune system was absent in cancer," Jhaveri says. "Today, however, we understand

RESEARCH SPOTLIGHT

TARGETED TESTING

New technologies are fueling advances in blood-based testing (liquid biopsies) to pick up signs of abnormally growing cancer cells, which is broadening screening for genetic signatures of cancer. It's part of the evolution toward more personalized, patient-specific care that will mean diagnoses and the right treatments will be better matched to patients. At Intermountain Healthcare in Utah, researchers found that such a precision-medicine approach helped patients live longer on average and cost the health system less than traditional strategies for people with advanced cancer. "We see doubling of overall survival, and cost savings of $750 on average per patient," says Dr. Lincoln Nadauld, vice president and chief of precision health and academics at Intermountain.

—Alice Park



The invention of 3D mammography—versus 2D—is lowering the rate of false positives.

RESEARCH SPOTLIGHT

DE-ESCALATING TREATMENT

Ductal carcinoma in situ (DCIS) is among the earliest stages of breast cancer. It doesn't appear to grow quickly and only about 20% to 30% of DCIS progresses to become invasive breast cancer, yet many women diagnosed with DCIS will get invasive treatment in the form of surgery, radiation or a combination of both. Dr. Shelley Hwang, chief of breast cancer surgery at Duke University School of Medicine, is hoping to change this. Hwang's study, COMET (Comparison of Operative Versus Monitoring and Endocrine Therapy), is designed to compare what happens to women who monitor their DCIS carefully with regular screening and scans, compared to those who get the standard treatment. The idea of watching a cancer, rather than taking immediate action to treat it, is a difficult one for patients and doctors alike to accept. "The challenge is to pull the rest of society with us in saying we now have biomarkers, we have data and we have clinical trials to show that a lot of the things we were doing in the past we did because we thought we had to, but we don't really need to do everything," Hwang says. "And I think the place to start doing that is in very low-risk conditions like DCIS." —*A.P.*



RESEARCH SPOTLIGHT

CHECKMATE FOR ONE DISEASE?

In June, a study in the *New England Journal of Medicine* claimed unheard-of results: All 12 subjects in the trial had experienced 100% remission of early-stage rectal cancer and have remained cancer-free for two years to date. The magic bullet? A type of immunotherapy called checkpoint inhibitors.

The drugs target proteins on T cells that are called checkpoints. If the T cells find something to fight, they turn those checkpoints on. When they're no longer needed, the T cells turn them off to avoid harming normal cells. Trouble is, cancer cells have found a way to keep checkpoints turned off, which prevents the immune system from attacking and killing them. "Checkpoint inhibitors block checkpoints, which takes the brakes off the T cells so they can then attack cancer cells," explains Dr. Michael Zinner.

This study was significant for several reasons. "We've never seen a trial where 100% of patients responded," Zinner says. The study is also unique in that the inhibitors were used alone—without surgery, radiation or chemotherapy.

The therapy was for a not-so-common type of rectal cancer and the sample size was very small, so more research is needed.

Cells have all sorts of ways to communicate with each other. Checkpoints are one area that researchers are exploring.



Surviving cancer is one thing, but approximately two-thirds of patients will have to deal with "late effects" of treatments they had. This includes problems down the road with other organs, including the brain, heart and lungs.

that cancer has mechanisms to work around and hide from the immune system, which has opened the door to new treatments." Immunotherapy is used to treat many types of cancer, including melanoma and lung, kidney, colorectal, and head and neck cancers. Researchers are trying to understand why this approach can be so beneficial for some people but not for others.

LOOKING AHEAD

While the current cancer treatment landscape should give anybody hope, the future looks even brighter. "There's never been a better time for treating cancers and it's only going to get better," Zinner says, adding that the Food and Drug Administration is approving between 10 and 15 new cancer treatments every year. "That's more than for other diseases we treat."

All of this aligns with the Cancer Moonshot initiative, which was introduced by the Biden-Harris administration in February 2022. One of its goals is to cut cancer death rates by at least 50% over the next 25 years and prioritize cancer screenings. But while there are screening innovations constantly going on behind the scenes, "developing a screening tool that's highly accurate for each cancer is difficult, as too many false positives are costly, often requiring more—and unnecessary—invasive testing," Jhaveri says. And for some types, like ovarian cancer, surgery is often the only way to confirm the presence of cancer. The other hitch is that many people aren't getting the recommended screenings, even though they're covered by insurance (this was true before the pandemic as well).

So what does all of this mean for the Cancer Moonshot, especially in terms of cutting death rates? "If we can focus on prevention and screening and then treating, especially in the early stages, we should be able to achieve the goal," Jhaveri says.

RESEARCH SPOTLIGHT

KICKING OUT GUESTS

Shannon Mumenthaler, PhD, assistant professor of medicine at the Keck School of Medicine of the University of Southern California and chief translational research officer at the Ellison Institute for Transformative Medicine in Los Angeles, heads a team focused on understanding the biological homes that cancer cells find in the body. The hope is that by making this environment less hospitable, it will open up entirely new ways to treat the disease. Eventually, such improvements in treatment will spill over into preventing cancer as well. The better researchers get at identifying the key drivers of cancer, and which risk factors are the hallmark of more aggressive disease, the sooner they can start looking for these among their patients and refine how their health is monitored for signs of the devastating disease. *—A.P.*



Researchers are exploring how a gene called DLGAP2 is related to a loss of working memory in humans.

'AMYLOID IS STILL IMPORTANT, BUT IT'S ONLY ONE PART OF THE ALZHEIMER'S PUZZLE.'

—Dr. Matthew Peters



The Alzheimer's Grind

With few breakthroughs in sight, researchers are doggedly pursuing all possible approaches to find a way to treat this disease.

By Stephanie Watson

When Dr. Eva Feldman, moved her 88-year-old mother into a Michigan memory care unit five years ago, she thought she knew everything there was to know about Alzheimer's disease. Still, the neurologist and neurodegenerative disease expert was shocked by the number of ways in which Alzheimer's devastates lives. Some residents sat immobile in their wheelchairs, unable to communicate or even feed themselves. Others walked and talked with ease but had no idea who they were or what they were doing there.

"It was so sad to see the loss in these once vibrant people," recalls Feldman, who is the Russell N. DeJong professor of neurology at the University of Michigan. "This disease robs you of your very essence. Not only your mind and your personality, but your very essence."

Her mother has since passed, but the 11 months that Feldman spent visiting her in that memory care unit reshaped her research. Renowned for her groundbreaking work on amyotrophic lateral sclerosis (ALS), she now devotes half of her NeuroNetwork for Emerging Therapies lab to brain health and Alzheimer's prevention.

One area of her research focuses on stem cells, the raw materials for heart and skin cells as well as the nerve cells (neurons) that make up the brain's communication network, which Alzheimer's destroys. Feldman and her team have already shown that transplanting stem cells into the hippocampus—the brain's learning and memory center—improves cognition in mice bred to mimic Alzheimer's disease. Still to be determined is whether these results can be replicated in humans.

GATHERING CLUES

Feldman is just one of many researchers around the world trying to fit together the pieces of the Alzheimer's puzzle and offer hope to the estimated 6.5 million people living with the disease—and the millions more who are at risk.

The complexity of this disease and its many subtypes have made Alzheimer's particularly challenging for researchers to study. Dr. Russell Swerdlow, director of the University of Kansas Alzheimer's Disease Research Center, likens it to the parable about six blind men trying to imagine what an elephant looks like by each feeling one piece of the animal. "We're all



Up to 18% of people age 60 or older have mild cognitive impairment, a potential precursor to Alzheimer's.

appreciating different parts of the elephant and coming to different conclusions about what those parts represent. And it's been a real struggle to put the different pieces together so that we can clearly recognize the elephant," he says.

The foremost clue to what form Alzheimer's takes is a sticky protein called beta-amyloid. The amyloid hypothesis, which has been the prevailing explanation behind Alzheimer's development for more than two decades, posits that beta-amyloid clumps together to form deposits called plaques in the brain. Plaques disrupt communication between neurons and ultimately lead to their death. Beta-amyloid works in concert with a threadlike protein called tau that forms tangles inside neurons and jumbles the communication signals between them.

If the buildup of beta-amyloid and tau are responsible for gradual neuron destruction and subsequent memory loss as this hypothesis suggests, then the most obvious solution would be to clear these destructive proteins from the brain, right? Not necessarily. Several monoclonal antibody drugs directed against beta-amyloid have failed in clinical trials. Though some of these therapies did clear beta-amyloid from participants' brains, they didn't slow cognitive decline or change the course of the disease—the holy grail of Alzheimer's research.

The one monoclonal antibody drug that finally did achieve Food and Drug Administration approval, aducanumab (Aduhelm), has been mired in controversy for having no (or a murky) effect on patient outcomes, despite its $28,200 annual price tag. (See page 55 for more on Aduhelm.) Then, in July, came allegations that the landmark 2006 study directly linking beta-amyloid buildup to memory loss and substantiating the central amyloid hypothesis (it wasn't the first to implicate beta-amyloid) might have contained doctored images, casting doubt on a concept that spawned millions of dollars in research funding.

Could this be the death knell for the amyloid hypothesis? Not necessarily, says Dr. Matthew Peters, associate professor in the department of psychiatry and behavioral sciences at Johns Hopkins Medicine. "What we're learning from the trials is that amyloid is a main component that drives the pathology of the disease, but it's only one part of the story." Like kindling, amyloid ignites changes in the brain that cause neurons to die. That triggers the release of other chemicals and proteins, creating a sort of chain reaction that unleashes a firestorm of damage. Once the process starts, even if amyloid is eliminated, "the fire can rage on," he says.

If amyloid is to play any role in Alzheimer's treatment, timing will be key. The research so far has involved people who were already showing symptoms, which means their brains had already been accumulating beta-amyloid and tau for many years. By then it may be too late to reverse or slow neuronal damage with anti-amyloid therapy alone, says Dr. Reisa Sperling, director of the Center for Alzheimer Research and Treatment at Mass General Brigham, in Boston. She believes we'll have more definitive answers in the next couple of years, as trials testing antibody therapies earlier in the disease come to fruition. "If all these trials fail…then clearly we are not thinking about this right," she says.

LEAVING THE BOX BEHIND

To detect Alzheimer's brain changes before symptoms appear requires a more convenient and cost-effective test than the positron-emission tomography (PET) scans and spinal fluid tests currently used in research. A biomarker test that detects amyloid changes in the blood already exists and has been granted breakthrough designation by the FDA, although it's not approved yet. It's conceivable



Lifestyle habits, like exercise, a healthy diet and maintaining social connections, are still considered to be excellent ways to try to prevent the onset of Alzheimer's.

'IN THE FUTURE, A BLOOD TEST COULD ALERT US TO ELEVATED AMYLOID LEVELS AND THEN WE COULD TAKE A DRUG TO REDUCE IT.'

—Dr. John Morris



Staying social and challenging the brain with new activities elevates levels of brain-derived neurotrophic factors, which have been characterized as being like fertilizer for neurons, helping to spur the growth of new connections.

that a blood test might one day detect dementia risk, just like the ones that currently identify diabetes and heart disease risks. "We could get a blood test in our 50s, and if it shows abnormal amyloid levels, conceivably take a drug that reduces amyloid in the hope of delaying the onset of Alzheimer's dementia or even preventing it," says Dr. John Morris, director of the Knight Alzheimer's Disease Research Center at Washington University School of Medicine, in St. Louis.

Alzheimer's is unlikely to be a single protein or a single pathway disease, says Swerdlow. "Solving this is going to require some out-of-the-box thinking." Both he and Sperling envision a future in which Alzheimer's treatment targets the disease from multiple angles with multiple therapies, similar to the way we now treat cancer (with surgery, chemotherapy, and immunotherapy).

Along with antibody therapies against beta-amyloid and tau, here are a few other areas researchers are investigating to protect neurons and prevent Alzheimer's damage.

Inflammation This is the third key piece of the Alzheimer's puzzle, along with amyloid and tau. A decade ago, researchers thought that dampening inflammation was the key to combating amyloid and tau buildup. They've since discovered that inflammation early in the disease actually clears out these harmful proteins. It only becomes harmful in the later stages, which may be why steroids and other anti-inflammatory treatments investigated have so far been a bust. The question is how we might modulate the immune system differently at each stage of the disease, Sperling says.

Mitochondria A decline in function of these cellular energy generators is a hallmark of the aging process, as they serve as tiny biological

clocks. Swerdlow is studying how mitochondria might contribute to or be altered by Alzheimer's plaques and tangles, and whether therapies that turn back the clock on these organelles could slow or reverse the disease.

Microbiome The gut is like a miniature city teeming with billions of microorganisms. Early research suggests that disruptions in the microbiome might trigger inflammation that drives dementia. Dietary approaches, including probiotics to alter the microbiome population and the very low-carb, high-fat ketogenic diet could be one way to delay neuron degeneration.

The current state of Alzheimer's research, which is happening around the globe, is about where cancer research was in the 1950s, says Miranda Orr, PhD, assistant professor of internal medicine in the Wake Forest University School of Medicine, in Winston-Salem, North Carolina. Scientists are just starting to grasp the full complexity of the disease and how to combat it. When she entered the research field after watching her grandmother decline from the disease, Orr had a lofty aim: to find a cure for Alzheimer's. Her goals today are more realistic and incremental. She believes we will make inroads by tackling the disease with different approaches, just as we have with cancer. Her own research focuses on ways to clear cellular senescence—damaged cells that promote inflammation and appear to accelerate cognitive decline. "I don't know if we'll ever fully prevent Alzheimer's…but I think we will succeed at delaying onset and having some disease-modifying therapies in our lifetime," she says.

Stephanie Watson is a freelance writer who has covered consumer health for more than a decade.

FROM THE *TIME* VAULT

The Aduhelm Controversy

IS ANYTHING BETTER THAN NOTHING WHEN IT COMES TO TACKLING BETA-AMYLOID?

In theory, the approval of the first drug to treat Alzheimer's disease would be cause for universal celebration. But ever since the FDA gave aducanumab (brand name Aduhelm) the go-ahead in 2021, it has been mired in controversy.

Two drug trials, from manufacturers Biogen and Eisai, were originally deemed unsuccessful, but then a subsequent analysis showed some promise for the drug, as well as some serious side effects. Against recommendations from its independent advisory committee, the FDA approved aducanumab under its accelerated approval program. (Accelerated approval allows the agency to approve a drug based on a single positive study and other evidence in situations where there is an unmet need for treatments—an understatement when it comes to Alzheimer's.)

Since then, the U.S. Department of Health and Human Services Inspector General announced that it would look into allegations that the FDA had an "inappropriately close relationship" with the pharmaceutical industry. The FDA is also requiring an additional trial to confirm the drug's benefits, which is expected to take at least four years.

Meanwhile, earlier this year, the Centers for Medicare and Medicaid Services, which controls what these government funded programs will cover—and influences private insurers' policies as well—said it will only cover aducanumab if the patient is part of an approved clinical study.

Groups like UsAgainstAlzheimer's and the Alzheimer's Association maintain the drug should be covered and prescribed since there are so few alternatives. Current drugs only address the symptoms of the condition, while aducanumab attacks amyloid plaques in the brain, targeting what is believed to be one of the causes of the disease.

"There are additional drugs nearing the end of their clinical trials and until we see the data we can't be sure what those will show," says Russ Paulsen, COO of UsAgainstAlzheimer's. "Patients and their caregivers are still waiting for an effective Alzheimer's treatment that they can have access to before it's too late. But a thousand people a day progress from mild to moderate Alzheimer's and almost nothing in the pipeline that we know of is targeting those later phases." *—Alice Park, Tara Law and Janet Lee; updated excerpt from* TIME, *Aug. 5, 2021*



New treatments are focused on keeping this amazing pump and its vessels working as they should so blood can flow freely.

New Help for Heart Disease

Innovations in treatments and care are making it easier to live longer with this No. 1 killer.

By Deborah Skolnik

When it comes to causes of death in the U.S., heart disease sits atop the grim heap: Someone dies every 34 seconds from it, according to Centers for Disease Control and Prevention statistics. The COVID-19 pandemic only made the numbers worse: A study published in 2022 in *Nature Medicine* compared more than 150,000 veterans who had recovered from COVID-19 with a similar but uninfected group. They found that the risk of cardiovascular problems in the COVID-19 survivors was significantly elevated for at least a year post-infection, even for those who didn't have underlying risk factors.

While researchers continue to explore the mechanisms for this elevated risk, there is good news about efforts to knock America's No. 1 killer off its perch. The biggest shift is that a diagnosis of heart trouble no longer necessarily means your life will be cut short. "People still die of it, but instead of dying in their 60s or 70s, many are now easily staying alive until their 90s or even reaching 100," says Dr. Mario J. Garcia, chief of the division of cardiology and co-director of the Montefiore Einstein Center for Heart and Vascular Care, in the Bronx, New York. "Research is one of the many factors behind this improvement," he shares. New medications, surgical procedures and game-changing studies are leading the charge to treat heart disease even more effectively.

NEW CHOLESTEROL-LOWERING OPTIONS

About 20% of people can't tolerate statins, drugs prescribed to lower cholesterol levels, and 40 to 75% discontinue their statin use within one to two years of starting them, according to a review in the *American Journal of Cardiovascular Drugs*. Some relatively new classes of drugs present a work-around. The first of these are PCSK9 inhibitors. They go by the brand names Repatha and Praluent, and they lower cholesterol by reducing the liver's levels of PCSK9, a protein linked to high cholesterol. "In big trials they have had almost no side effects," says Dr. Amit Khera, a preventive cardiologist and professor at The University of Texas Southwestern Medical Center in Dallas. "They are injectable medicines given just every two weeks and they essentially cut your cholesterol in half or more."

Another type of PCSK9 inhibitor, called inclisiran (brand named Leqvio) is categorized as a "gene-silencing drug" because it works by affecting the genes that promote the production of PCSK9. The result: Less of it is made in the first place. Another advantage is that inclisiran doesn't have to be administered very often. "With two injections a year, you can reduce the cholesterol to really low values," says Garcia. "Right now there are trials going on to demonstrate that this approach can lower the risk of heart attacks." As you might expect, these drugs are pricey, but Medicare will cover them for many patients.

TREATING PROBLEMS AT THE SOURCE

Between 1990 and 2017 the number of people with heart failure almost doubled, according to a study published in 2021 in the *European Journal of Cardiology*. Heart failure occurs when the organ can no longer sufficiently pump enough blood through the body. The heart doesn't stop—it just doesn't work as well as it should. New research is increasing an understanding of the immune system's role in heart failure. "The condition starts with an injury to the heart, which can be a blockage of the coronary artery," explains Shyam Bansal, PhD, an investigator and assistant professor of physiology and cell biology with the Davis Heart and Lung Research Institute at The Ohio State University. "When there is a blockage, immune

cells, including T cells, try to heal the heart. When they can't, because that tissue is essentially dead, they enter a 'frustrated' state where they cause more inflammation, which only does more damage," he explains.

Bansal has created a drug that targets a protein within those errant T cells and stops them from proliferating. "When we do that, we see an improvement in cardiac function," he says. "We might be able to remove some patients from the heart-transplant list altogether, or maybe we can keep them going long enough so that a heart becomes available for them." The medication may be ready for Food and Drug Administration review as an "investigational new drug" in the next two to three years.

SURGICAL STEPS

With rising heart failure cases comes a greater need for heart transplants, but with new guidelines, the number of human hearts suitable for transplantation from donors is growing, says Garcia. "It used to be that we could only take the hearts of donors that were very healthy and young. Now we can take the organs of individuals who have chronic illnesses, because those can be treated," he says. "This expands the number of organs that are available, so we can do more transplants in individuals that can go on to live relatively normal lives." His hospital recently transplanted the heart of an HIV-positive donor into an HIV-positive patient.



New stent technology being researched would allow the device to gradually degrade and be reabsorbed into the body.

Surgical procedures aimed at treating heart arrhythmias, or irregular heartbeats, are improving, too. While they've long been treated with medications, patients would sometimes forget to take them, and some drugs caused unpleasant side effects such as tremors and nausea. Now, "interest in the drugs is waning," Garcia shares. Instead, the focus has turned to ablation, a surgical procedure that either burns or freezes parts of the interior of the heart to short-circuit the electrical signals that create irregular heartbeats. "There are advances in the equipment that is used to perform ablations, and they can be done safely and more effectively than ever," Garcia says. Plus, the surgical techniques of ablations have improved. "The likelihood that you would have a recurrence of fibrillations [rapid, irregular contractions of the heart's muscle fibers] is every year becoming less frequent," he notes.

Other surgical procedures are becoming less invasive, or utilizing more effective devices. Leaky heart valves, for instance, used to be swapped out via open-heart surgery. Now they can be advanced and implanted through a small puncture wound in the veins and arteries of the leg. For heart failure, a new device called an AccuCinch can be implanted via a catheter into the heart's lower left ventricle, which grows bigger and loses its ability to pump the proper amount of oxygenated blood to the rest of the body. Once implanted, the cinch is closed, reducing the size of the left ventricle as well as valve leakage, and strengthening the heart wall.

With advances in prevention and treatment, science is slowly beating back heart disease. "There's no question that we are making progress," says Khera. "I'm an optimist."

Deborah Skolnik is a New York–based health writer.

FROM THE *TIME* VAULT

Diabetes and Cardiovascular Events

SCIENCE SHOWS THAT THE CONDITION MAKES A HOST OF HEART-HEALTH ISSUES WORSE.

If you've been diagnosed with diabetes, you've got plenty of company. The American Diabetes Association (ADA) reports that in 2019, the most recent year for which data is available, about 11.3% of the population had the chronic condition.

Over time, elevated blood-sugar levels spell trouble for the entire body, says Dr. Joshua Joseph, an endocrinologist with The Ohio State University Wexner Medical Center in Columbus. "High levels of blood sugar damage the small and large vessels in the body," including those around the heart, leading to heart disease, he says. Elevated glucose can also harm the nerves that control the heart.

Diabetes is correlated with a heightened risk of major cardiac events, such as stroke, heart attack and death. Plus, the longer people have diabetes, the more likely they are to develop heart disease, according to the National Institutes of Health.

People with Type 1 diabetes may have a lower risk of heart complications than those with Type 2. That's because they're less likely to be overweight or obese, which can increase the risk of heart problems, says Dr. Robert Gabbay, chief scientist and medical officer of the ADA. It's not entirely clear how the two are connected, but there are likely several factors involved.

COMORBIDITIES

People with diabetes are more likely to have other conditions, such as high blood pressure and cholesterol, and obesity, that independently increase the risk of heart disease, says Gabbay. "When you start adding those together, the risk starts multiplying," he says.

SYSTEMIC INFLAMMATION

High blood sugar can "lead to a variety of inflammatory states and microvascular disease, or small blood vessel disease," explains Dr. Andrew Freeman, a cardiologist at National Jewish Health in Denver. "The very same environment that helps create diabetes helps to create cardiovascular disease, and vice versa." Systemic inflammation stemming from high blood sugar can lead to blood clots, stroke and heart attack.



Regular exercise lowers diabetes risk.

INSULIN RESISTANCE

Obesity is related to insulin resistance, which means your muscles, liver and fat cells don't respond well to insulin and aren't able to use the glucose in your blood to fuel their functions. Insulin resistance, sometimes called prediabetes, can develop into Type 2 diabetes. "Insulin resistance is associated with all sorts of other bad things, and one of these is inflammation," Gabbay says.

MEDICATIONS

Two new classes show promise in treating glucose levels in people with Type 2 diabetes: GLP-1 receptor agonists and SGLT-2 inhibitors. Gabbay says they "have been shown to reduce heart disease and cardiovascular mortality but they're underutilized." People with poor blood glucose management would benefit the most, and of that group, only about 15% are using these medications. —*Elaine Howley, excerpted from* TIME*, July 20, 2022*

THE INVISIBLE CRISIS

A Perfect Storm

America's collective mental health had been spiraling downward for more than a decade. Then COVID-19 hit.

By Katherine Cullen



Among all the disturbing headlines this year, one was especially alarming. In a study of almost 175,000 children through age 17, anxiety and depression diagnoses had climbed 29% and 24%, respectively, between 2016 and 2019. Published this spring in *JAMA Pediatrics*, the study analyzed data collected by the National Survey of Children's Health. COVID-19, not surprisingly, worsened these statistics. It was one of many that have quantified what mental health experts had already been seeing since 2010: an alarming rise in childhood mental health concerns and suicide, prompting the American Academy of Pediatrics to declare a national youth mental health care emergency in 2021.

Of course, adults aren't faring any better: According to Census Bureau data, approximately 36% of respondents reported anxiety and depression symptoms in July 2020—up from 10% in 2019—with many (especially those with less education or disabilities, people of mixed race and women) still distressed today. Health care workers, whose levels of burnout had already reached crisis levels before the pandemic, have experienced increased anxiety, depression and post-traumatic stress disorder (PTSD) as well (see page 64).

What's behind this sustained emotional anguish—and is the pandemic solely to blame?

WHERE IT ALL BEGAN

"Today's mental health crisis arguably dates to the 1980s, when federal budget cuts deprived millions of Americans with mental illnesses from critical social welfare and community mental health services," says Dr. Thomas Insel, former director of the National Institute of Mental Health and executive chair of the San Francisco-based mental health platform Vanna. Death and disability rates, especially for people with severe mental illnesses, rose—despite improvements in treatment—while a patchwork mental health care system designed to alleviate symptoms and manage crises rather than promote recovery took shape. Ongoing disparities in availability and insurance coverage of mental health care, coupled with inconsistencies in care quality, mean too many people still remain

Mood disorders are the most common cause of hospitalization for people under age 45, after pregnancy and birth, according to the National Alliance on Mental Illness.



untreated, says Insel, who's also the author of *Healing: Our Path from Mental Illness to Mental Health.*

Rising economic inequality in recent decades (which, research shows, increases the risk of poor mental health) plus underinvestment in factors known to protect well-being (think: safe, affordable housing, education and nutrition) also play a role, Insel adds.

Research by Jean Twenge, PhD, a professor of psychology at San Diego State University, suggests social media may be another trigger for mental health problems, especially among adolescents. The sensory bombardment, upward comparisons, and outrage its algorithms breed help explain the link, says Roger K. McFillin, PsyD, a clinical psychologist at the Center for Integrated Behavioral Health in Bethlehem, Pennsylvania.

THE PANDEMIC'S EFFECT

Cue the pandemic, which left more than 19% of Americans grieving loved ones (the majority Black or Hispanic, according to University of Chicago surveys), amplified pervasive uncertainty and saw one in 13 adults infected by COVID-19 develop chronic symptoms, per Centers for Disease Control and Prevention data. Add lockdowns, which upended work, school and social routines; worsened social isolation; barred grieving people from participating in mourning rituals and shuttered places of worship; restricted access to medical care; and increased unemployment. It also worsened economic insecurity for tens of millions of people. Throw in confusion created by virus and vaccine misinformation plus a volatile political climate, and Americans' mental health further plummeted, says Corey Nigro, PsyD, a clinical neuropsychologist at InwardBoundPsych in Duxbury, Massachusetts. Mental health providers were overwhelmed with inquiries and many couldn't accept

FROM THE *TIME* VAULT

Teletherapy's Promise and Problems

DESPITE WIDER ACCESS, VIRTUAL MENTAL HEALTH TREATMENT IS STILL OUT OF REACH FOR MANY.

For years, advocates have argued that teletherapy could make counseling more accessible and convenient. The hope was that virtual therapy could help democratize a system that allowed almost 20% of white Americans to receive mental health care in 2019, but fewer than 10% of people identifying as Black, Hispanic, Asian or Pacific Islander.

While telehealth has certainly improved mental health care access during the pandemic, the same problems that kept many people from seeking care before the pandemic still exist. As a result, mental health usage in the U.S. hasn't changed as drastically as many advocates would have liked.

One reason is the financial barrier: A single therapy session can easily top $100 (without insurance), and telehealth has done little to change that. Another limitation: There are simply not enough therapists to go around—and not enough from diverse backgrounds. A 2020 study concluded that just 10% of U.S. psychiatrists identify as Black, Hispanic, American Indian, Alaska Native, Native Hawaiian or Pacific Islander. "There are many patients who want a Black therapist and they can't get it," says Dr. Amanda Calhoun, a psychiatry resident at Yale and a fellow on the American Psychiatric Association's Council on Minority Mental Health and Health Disparities. "If we truly want to reduce the gap [in mental health care usage] we need to make it a trustworthy system where people feel they can connect with their therapist."

And it appears telemental health access is expanding permanently. The PSYPACT (Psychology Interjurisdictional Compact) agreement allows therapists in 35 states to practice across state lines (with other PSYPACT states). And in 2021, Congress permanently expanded coverage of telehealth services for Medicare holders, almost 10% of whom live under the poverty line.

—Excerpted from TIME, *June 14, 2022*



A Pew Research Center study found that 7% of Americans don't use the internet at all, so telehealth isn't an option for everyone.

new clients due to already full schedules, American Psychological Association surveys show.

THE PATH FORWARD

The adoption of telemental health in most states has helped address the crisis, says Nigro, but it's no panacea (see sidebar at left for more). But interstate service delivery legislative proposals such as PSYPACT, the Psychology Interjurisdictional Compact, which allows practitioners to see patients across state lines, plus new federal funding for community behavioral health clinics and a national 988 crisis hotline, offer hope. So do 12-step meetings, noncrisis "warm" lines and support groups.

Modernized electroconvulsive therapy (ECT) and ketamine-assisted therapy are two innovative approaches to treating severe conditions, like treatment-resistant depression, says Nigro. Other approaches, like psychedelic-assisted therapy with psilocybin and MDMA, are being investigated. But none of them are without risk. Regional transcranial magnetic stimulation (rTMS) offers a less invasive alternative to ECT while a *Frontiers in Psychiatry* analysis suggests exposure to high temperatures (heat therapy) and ketogenic diets may reduce depression and schizophrenia symptoms comparable to pharmaceuticals—with fewer side effects. (More research is needed.)

Many effective treatments aren't new. Numerous studies have found that cognitive behavioral therapy (CBT), designed to change self-defeating thoughts and behaviors; dialectical behavior therapy (DBT), which teaches mindfulness, emotion regulation, distress tolerance and interpersonal skills; and acceptance and commitment therapy (ACT), which encourages accepting emotions, developing coping skills, and focusing on meaningful activities, can lower suicidal ideation and self-harm, reduce anxiety and depression, and improve coping and psychotic symptoms.

Experts emphasize that treating anxiety and depression requires more than therapy and pharmaceuticals. "Social connectedness, access to safe and supportive living spaces, and a sense of purpose are key elements of recovery," Insel says. Equally important, adds McFillin, are "lifestyle changes, like eating more nutrient dense foods, getting better sleep and spending less time on screens." But many people live in environments where they don't have easy access to healthy, affordable food and where stress impedes sleep.

Improvements won't happen overnight, cautions Insel, but new federal mandates and funding to increase mental health service access are a good start. And ongoing efforts to address the social, environmental and policy forces influencing mental health outcomes have him hopeful a brighter future is on the horizon.

Katherine Cullen, MFA, LMSW, is a social worker and freelance writer based in New York City.



FROM THE *TIME* VAULT

Healing the Healers

Psychedelics have the potential to alleviate symptoms of stress, burnout and depression.

By Shoshana Ungerleider

From Wall Street to Hollywood, psychedelics are having a cultural moment. For those of us who grew up in the "This is your brain on drugs" era, it's hard to let go of the stigma—and the mental image of an egg sizzling in a pan. But as a growing number of states and cities move to decriminalize drugs, and investors flock to an emerging market for psychedelic health care, substances like psilocybin, ketamine and LSD are edging into mainstream culture—and setting the stage for a paradigm shift in modern medicine.

Within the next few years, we could see psychedelic therapies prescribed for refractory depression and post-traumatic stress disorder, or used in palliative care for those facing a life-limiting illness. But first we need to more deeply understand the benefits of psychedelic treatments. We are in the perfect storm to accelerate continued study—and health care workers are in the thick of it.

It's no coincidence that psychedelics are entering the conversation just when we most sorely need new ideas in mental health care. The world is experiencing mass trauma from COVID-19. It'll take years for us to truly understand the magnitude of the pandemic's toll on our collective mental health, but on the front lines, the picture is much clearer. In a 2021 survey of more than 20,000 front-line medical workers, 38% reported experiencing anxiety or

depression during the pandemic, and 49% suffered burnout. Another survey found nearly one-quarter of all health care workers showed signs of probable PTSD. When the American Association of Critical-Care Nurses surveyed 6,000 of their members the same year, 66% said they had considered leaving their jobs because of the pandemic.

Among health care workers, the prolonged battle against COVID-19 has intensified a long smoldering problem. Facing a fragmented medical system with frequently misaligned incentives, health care workers have been grappling with anxiety and depression—even before COVID, the suicide rate among doctors was more than twice that of the general public. From support groups and training to apps that monitor mental health, there are a number of programs that aim to solve and treat the problems leading to clinician burnout. But most have barely scratched the surface, and the prevalence of burnout during the pandemic has led researchers to explore alternative solutions—including psychedelic therapies. A new study at the University of Washington is evaluating the efficacy of psychedelic-assisted psychotherapy using psilocybin for front-line health care workers experiencing COVID-related distress.

The U.S. is not alone in seeking alternative therapies for the growing number of health care workers in crisis: At Vancouver Island University in Canada, the Roots to Thrive ketamine-assisted therapy program treats health care providers and first responders with PTSD, depression, anxiety and addiction.

Realizing the potential of psychedelic-assisted therapy with health care workers is not without its challenges. For medical professionals, there's a culture of perfectionism that makes asking for help a sign of weakness. Just past these barriers and stigmas, however, there's enormous potential. If these studies and programs are successful, they have the ability to alleviate the symptoms of stress, burnout and depression that health care workers are feeling. They may even stop medical professionals from leaving the workforce at an alarming rate and avert the looming disaster of a worldwide shortage of health care workers. It's a win-win. Everyone can potentially benefit from better health care outcomes, since the pandemic's toll on health care workers affects the level of care that they're able to provide.

If psychedelic treatments have the potential to alleviate any person's suffering, they are worth studying. We need to invest in studying them further and faster.

—Excerpted from TIME, *Oct. 13, 2021*

Dr. Shoshana Ungerleider is an internal-medicine physician in San Francisco, host of the TED Health podcast and founder of endwellproject.org.

FROM THE *TIME* VAULT

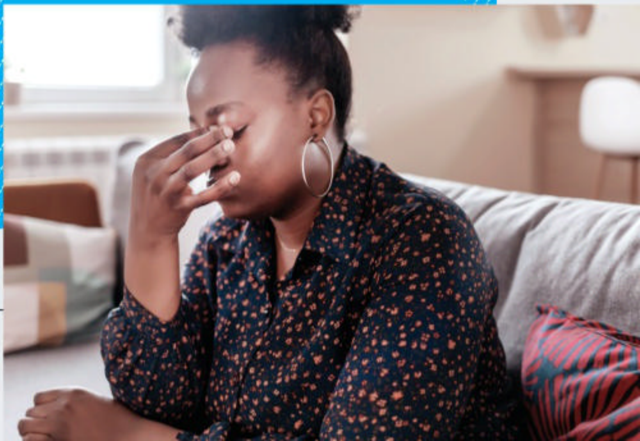
The Diabetes-Mental Health Connection

HAVING ONE INCREASES THE RISK OF THE OTHER.

Living with a mental health disorder is challenging enough without adding physical ailments to the mix. But recent research suggests that people with psychiatric disorders also have higher rates of Type 2 diabetes (T2D), and the combination can be devastating.

In a large meta-analysis, a team from the University of Southern Denmark found much higher T2D rates in people with psychiatric disorders, including a 15% higher rate in those with substance-use disorder, 13% in anxiety disorder and 11% in those with bipolar disorder. What's more, the association between T2D and psychiatric disorders goes both ways.

As the mechanisms underlying these links becomes clearer, doctors are starting to integrate the treatment of these diseases. "Some studies show that by treating depression aggressively, you can improve people's diabetes control so it's really quite exciting," says Anne Doherty, an associate professor of psychiatry at University College Dublin. —*Sandeep Ravindran, excerpted from* TIME, *March 10, 2022*



FROM THE *TIME* VAULT

A Therapeutic Breakthrough for Addiction

Psilocybin shows promise for substance abuse as well as other mental health disorders.

By Tara Law

To the uninitiated, psilocybin—the substance that gives "magic mushrooms" their psychedelic qualities—could be dismissed as a recreational drug. Like many other psychedelics, it is banned by the U.S. government as a Schedule 1 substance, meaning it supposedly has high potential for abuse and no currently accepted medical use in treatment. However, to many medical science researchers, psilocybin is much more: a promising treatment for a range of health issues. In particular, experts increasingly see the chemical as a potentially effective, low-risk tool to help patients break their dependencies on other substances. Given that more than 100,000 people died after overdosing on opioids and other drugs in the U.S. in 2021, it's an understatement to say it's urgent to find new, effective treatments for substance use disorder.

The research supporting psilocybin's use in this context has been growing for a while now. One of the most recent such studies, published in *Scientific Reports* on April 7, looked at data from 214,505 U.S. adults in the National Survey on Drug Use and Health (NSDUH) from 2015 to 2019, and found an association between past use of psilocybin—at any time in their lives—and a reduced risk of opioid use disorder. This kind of study doesn't show proof, only correlations, and there may be social or personal characteristics that make psilocybin users different from people who didn't decide to use the drug, says Grant Jones, a graduate researcher at Harvard University who co-authored the study. "Maybe there's different psychological profiles that make [some people] more immune to developing substance use disorders; we don't know," says Jones.

Nevertheless, the study adds to growing evidence that psilocybin is worth investigating as a treatment for substance use disorder, including for nicotine, cocaine, marijuana and opioids. Additional research has shown another potential therapeutic use of psilocybin: to assuage depression. For instance, a small randomized clinical trial published in *JAMA Psychiatry* in 2020, found that psilocybin-assisted therapy caused a rapid reduction in the symptoms of major depression symptoms, and that the effects remained statistically significant at least four weeks later. In another study co-authored by Jones, published earlier this year in the *Journal of Psychopharmacology*, he and colleague Matthew K. Nock reviewed NSDUH data, and found that psilocybin use was associated with a reduced risk of major depressive episodes.

Despite all that, Jones acknowledges that there's still a lot to learn about psychedelics. "The thing that always strikes me about psychedelic research is that even though there's an immense amount of excitement, and a lot of attention, and a lot of financial support that's flowing into the space, the actual body of literature is still very sparse," Jones said. "I think we're exploring the boundaries of the benefits of well-being."

'SCIENCE HAS REACHED A FIRST TIPPING POINT WHERE THERE'S NOW ENOUGH EVIDENCE [THAT] IT'S REALLY HARD NOT TO TAKE THE POTENTIAL OF PSYCHEDELICS SERIOUSLY.'

—Dr. Michael Bogenschutz



Only about 6% of people suffering with alcoholism get the care they need, according to a Washington University School of Medicine study.

THE KEY TO UNLOCKING DEPENDENCIES

Several clinical trials focused on mental illnesses like depression have shown that psilocybin appears to boost patients' moods even weeks after taking the drug. Exactly how remains uncertain, but researchers have a few ideas. Psilocybin appears to increase the brain's neuroplasticity—the ability for neural networks to shift and rewire. In a study published last April in *Nature Medicine*, researchers found that psilocybin helped to broadly build more connections between different parts of the brain, while simultaneously reducing interactions between brain areas connected with depression. In research in both people and animals, psilocybin appears to make it easier to break out of habits and become more adaptive, says researcher Dr. Michael Bogenschutz, a professor of psychiatry at New York University Grossman School of Medicine. "It increases the capacity of the brain to change, and therefore for thinking and behavior to change."

Researchers point to two characteristics that make psilocybin an especially attractive potential treatment for mental health conditions. First, while it can trigger some dangerous side effects if not used in a controlled environment, it tends not to be addictive. Second, psilocybin can have long-lasting effects, which means people would only have to take it intermittently, putting them at a reduced risk from any side effects. "That's a huge advantage in terms of safety…compared to taking a pill every day and having that side effect profile follow you for months, possibly years, depending on how long you take it," says Matthew Johnson, PhD, a professor in psychedelics and consciousness at Johns Hopkins University.

In many ways, research on psilocybin's potential is still just beginning. At this point, only a relatively few clinical trials have been published on psilocybin as a treatment for any type of substance use disorder, and many of those trials have involved a very small number of participants. In 2021, the first federal grant for studying a psychedelic treatment in 50 years was awarded for a double-blind randomized trial looking into psilocybin as a smoking cessation tool.

In Bogenschutz's opinion, the psychology and physiology underlying addiction to any given substance has a lot in common with that driving addiction to other such dependencies. And that, he believes, is what makes psychedelics so promising a therapeutic for substance abuse. "Something about psychedelic treatment of addiction that is exciting, is that the ways we hope it will work are not really specific to any particular addiction," he says. "[These drugs] could represent a therapeutic breakthrough for alcohol use disorder, other addictions, mood and anxiety disorders—a whole host of conditions."

—Excerpted from TIME, *April 19, 2022*

Tara Law is a reporter at TIME.



Friends provide a self-esteem boost and a coping mechanism for dealing with stress.

Lifestyles of the Healthy and Wise

You don't need drugs, pricey MRIs or a genetic workup to outsmart chronic conditions.

By Janet Lee



It's obvious that the future of medicine will be about dialing in diagnoses with better screening and creating more powerful and precise treatments for all patients. But relying solely on algorithms and machines to improve outcomes ignores an area that has a huge impact on health. Lifestyle plays a huge role in many chronic conditions, such as heart disease, stroke, diabetes, and certain cancers, says Dr. Raja Jaber, an associate clinical professor of family medicine and director of the lifestyle and integrative medicine program at Stony Brook University's Renaissance School of Medicine, in New York. "In our country and even in the rest of the world, we have a lifestyle that promotes chronic diseases, and, unless we change that, the number of people who have these conditions will increase exponentially, as will health care spending."

Due to a lack of time or training, physicians often don't address lifestyle habits during office visits, says Dr. Phyllis MacGilvray, a family medicine physician and senior associate dean of academic affairs at University of South Carolina Greenville School of Medicine. But it's become so important that lifestyle medicine is now a specialty track in some medical schools. USC Greenville and Loma Linda University School of Medicine, in California, are the first two medical schools in the U.S. to have fully integrated lifestyle medicine programs, including offering lifestyle-focused electives and required courses and specialty training. "We have a young medical school. We're just finishing our first decade and we've offered it from the beginning," says MacGilvray. Through the program, new medical students learn about the power of lifestyle habits, specifically six components that have reams of research supporting their impact on health: a whole-food, plant-forward diet; exercise; restorative sleep; stress management; avoiding toxic substances and enjoying supportive relationships and social connections.

"Lifestyle interacts with genes," says Jaber. "Whatever you do—how you eat, move and even think, sends information to the system as a whole and that is translated into different genetic expression. Genes aren't set in stone. We change the expression of them, and by doing that, we change our physiology."

Here are some of the ways researchers are learning that key lifestyle factors have a definite impact on health.



The Mediterranean diet is an excellent example of a plant-forward way of eating that emphasizes vegetables, fruit, beans, healthy fats and herbs and spices, while limiting red meat.

A WHOLESOME DIET

Lifestyle medicine advocates eating a plant-forward (some meat is OK), whole-food diet, since it has solid research showing its benefits. A November 2021 research review, published in *Frontiers in Cardiovascular Medicine*, evaluated 13 studies that involved more than 410,000 people. Eating a plant-based diet was significantly associated with a lower risk of cardiovascular-related death and cardiovascular disease. A 2022 study in *Diabetologia* found that predominantly consuming plants reduced the risk of Type 2 diabetes—which accounts for 90% of diabetes cases—in people who were generally healthy.

Dietitians have been trying to get the word out about the importance of food as medicine for decades, and within the next few years it might finally pay off. The Medical Nutrition Therapy Act, which would expand Medicare reimbursement, allowing coverage for seeing a dietitian, is working its way through Congress. "It's ridiculous that they'd pay for a bypass surgery but not a person to see a dietitian to prevent a heart attack or shrink arterial plaques," says Lauri Wright, PhD, RDN, chair of the department of nutrition and dietetics at the University of North Florida, in Jacksonville, and a spokesperson for the Academy of Nutrition and Dietetics. Along with that, the nutrition field is seeing more specialization as well. There are dietitians who specialize in cardiology, kidney health, pediatrics, geriatrics and gastroenterology—so it's easier than ever to figure out how to eat to address one's specific health picture, says Wright.



Sticking to a regular sleep cycle—say 11 p.m. to 7 a.m.—is as important as getting adequate z's.

RESTORATIVE SLEEP

This June, for the first time, the American Heart Association added sleep to its heart health checklist. That's because chronic sleep disruption has been linked with high blood pressure and cholesterol, metabolic syndrome, diabetes, cardiovascular disease and colon cancer—and that's in otherwise healthy people. That doesn't bode well considering three in 10 Americans reported having problems in their daily life due to insomnia, according to a 2022 survey from the American Academy of Sleep Medicine.

One common cause of sleep disturbances is sleep apnea, a condition where you stop breathing for short periods during the night (sometimes hundreds of times). "There is an epidemic of sleep apnea," says Jaber, who points to obesity as a big culprit (more sensitive diagnostic criteria for the condition means it's being caught and diagnosed more frequently as well). "There's almost a two- to four-fold higher odds of having obstructive sleep apnea with weight gain," says Dr. Vaishnavi Kundel, an assistant professor of pulmonary, critical care and sleep medicine at the Icahn School of Medicine at Mount Sinai, in New York. "It can really lead to significant sleep fragmentation where you're not getting that nice deep consolidated sleep. That leads you to being tired and sleepy, and it affects concentration and mood. Several studies have shown it can result in increased inflammation and stress to the heart over time and potentially increase the risk of abnormal heart rhythms, heart disease and stroke." Awareness about sleep and its importance for health is stoking a boom in sleep medicine as a specialty.

EXERCISE

Being physically active, especially accumulating 150 minutes or more a week of moderate to vigorous intensity exercise, has been linked with numerous health benefits, including better brain, heart, liver, kidney and lung health. It helps improve sleep and mood, makes it easier to lose or maintain weight and reduces blood pressure and the risk of several types of cancer. Since 2009, when the American College of Sports Medicine (ACSM) first started its Exercise Is Medicine initiative, the group has been working to promote the concept of addressing physical activity and exercise within health care and connecting physicians and other providers with exercise professionals. "We are seeing more physicians discussing exercise as part of the prevention and treatment of chronic disease and the promotion of wellness in general," says Dr. Liz Joy, senior medical director of wellness and nutrition at Intermountain Healthcare in Utah and chair of the ACSM's Exercise Is Medicine Governance Board. "Increasingly we're understanding that sedentary behavior is an independent risk factor for premature mortality," says Joy. "Even if you can't exercise, we know that accumulating more light activity throughout the day decreases the risk of dying early. All movement counts."



Physical activity, including weight training, should be considered an integral part of a healthy lifestyle.

AVOIDING HARMFUL SUBSTANCES

During the pandemic, both cigarette and alcohol sales rose, which will add to the negative health impact from COVID-19, says MacGilvray. Everyone knows smoking contributes to a host of diseases, but research on alcohol has been back and forth. A new study published in March in *JAMA Network Open* is swinging the pendulum toward the teetotalling side again. It included more than 371,000 adults who averaged 9.2 drinks a week. The study found that people who had light to moderate alcohol consumption had the lowest heart disease risk, even compared to the nondrinkers. But the study also discerned that the moderate drinkers also had the healthiest lifestyles—including better diets and more physical activity—and those factors were responsible for the rosier benefits. In addition, the researchers found that even low levels of drinking (up to seven servings a week) carried an increased risk of cardiovascular disease. Another study of 36,000 adults from researchers at the University of Pennsylvania found that light to moderate alcohol consumption negatively impacted brain volume.



A recent study from Johns Hopkins Bloomberg School of Public Health looked at 9,500 people between the ages of 61 and 81. It found that smokers developed heart failure at twice the rate of nonsmokers. Former smokers' risk was also elevated.

MANAGING STRESS

If there is one word to describe the American public over the last few years it would be *stressed*. From viruses to politics to jobs to climate change to portfolio values, it's been one thing after another assaulting our collective nervous system. And all that stress is hard on the body. A 2022 review of research, published in *The American Journal of Medicine*, found that stress increases the risk of heart disease as well as having a heart attack or stroke.

"We also know that unmitigated stress leads to telomere shortening," says Dr. Kien Vuu, an assistant professor of health sciences at UCLA and author of *Thrive State: Your Blueprint for Optimal Health, Longevity, and Peak Performance*. Telomeres are the protective wrappings that cap the ends of chromosomes, which reside in cells. As telomeres become frayed, the cells die. Experts believe this damage may be why stress has such an impact. (Exercise, smoking, excess weight and mindfulness also affect telomere length, both positively and negatively.) A 2016 study in *Brain Behavior and Immunology* found that short-term psychological stress, including depression, anxiety and trauma, was associated with a small but significant decrease in telomere length, similar to the effect that obesity has on telomeres.

The authors speculated that long-term chronic stress may have a more significant impact on telomeres. Researchers are learning more about how early life stress—the kind associated with family trauma in childhood—affects the stress response and health in adulthood as well.



More and more people are discovering the feel-good, stress-reducing effects of mindfulness practices, including yoga and meditation. Mindfulness enhances focus and teaches you how to create distance between stressful events or thoughts and your response to them.

FROM THE *TIME* VAULT

The Advent of Social Prescribing

TAKE TWO DANCE CLASSES AND CALL THE DOCTOR IN THE MORNING.



Loneliness can be as toxic as smoking.

It took two years and nearly 50 emergency-room visits for Dr. Ardeshir Hashmi to realize he didn't need to prescribe pills for his 93-year-old patient's excruciating chest pains. He needed to prescribe ballroom dance.

Beginning in 2015, a tight, suffocating pressure in her rib cage would prompt Ruth—a pseudonym used for privacy—to call 911. Every two weeks, she arrived at Massachusetts General Hospital and after extensive testing, she'd receive negative test results. Hashmi, now the chair of geriatric innovation at Cleveland Clinic, was baffled as he talked to Ruth about the pain that had receded long before she arrived at the hospital.

Hashmi finally discovered that Ruth's grandson had left for college right before the vicious chest pains began. She was alone in a dark, empty house, and no one would drive her to the neighborhood dance studio anymore. The loneliness triggered panic attacks.

So Hashmi referred Ruth to a geriatric-care manager who would drive her to ballroom dance, accompany her as she swayed in her chair to swing, and reconnect her with her love of music and her friends. Her twice-a-month ambulance habit vanished.

Hashmi had, in effect, written Ruth a social prescription, in which a clinician refers a patient to a community or cultural activity such as an art club, music performance, dance class, volunteer activity or nature walk in order to bolster their mental and physical health.

RIPE FOR RESEARCH

As logical as the idea sounds, the body of evidence demonstrating its benefits for patients (translated into financial savings for the health care system) is still lacking. In 2015, *The Lancet* published a double-blind study that assigned 1,200 adults with early dementia to receive either general health advice or an intervention involving regular exercise, social interaction and a controlled diet. The intervention actually improved patients' cognitive function from their baseline level, while general health advice only slowed cognitive decline. In a meta-analysis of seven arts-based interventions for cancer patients, all patients reported improved well-being, and many experienced reduced stress and anxiety.

In the meantime, it's an intervention without negative side effects. Dan Morse, founder of Social Prescribing USA—an organization supporting the advancement of social prescribing in the U.S.—hosts online "happy hours" for advocates to build networks around social prescribing projects. Attendees range from physicians to music therapists to big-shot developers from Reddit and the National Institutes of Health. "Just think what could happen if there's 10 million more people volunteering in our country," said Morse at a recent gathering. "If there's 10 million more people finding their voice through the arts who are sharing their work and beauty with other people." *—Rachel Chen, excerpted from* TIME*, June 15, 2022*



The global maternal death rate is decreasing, according to the Gates Foundation, but it's still more than twice what the U.N.'s Sustainable Development Goals are aiming for.

[SECTION 3]

THE BIGGER PICTURE

In a connected world, public health trends and climate changes can make a big impact beyond a single nation's borders.



CLIMATE 911

How the Weather Will Impact Lives

All those natural disasters and heat waves have a direct effect on the types (and number) of conditions doctors will be treating in the future.

By Ginny Graves



For years, many people thought of climate change as a phenomenon that was taking a toll on the ozone or the Amazon rain forest—effects that, while worrisome, seemed remote and impersonal. Those days are over.

A 2020 United Nations global report, titled *The Human Cost of Disasters*, found that from 1980 to 2019, natural disasters caused by climate change, including floods, cyclones, hurricanes, winter storms, droughts, wildfires and extreme heat, killed more than 1.5 million people around the world and impacted the health and lives of more than 7 billion (the total global population stands at just under 8 billion). What's more, between 2000 and 2019 there were 6,681 of these climate change-related extreme weather events (EWEs)—a "staggering rise" from the previous 20-year period.

With this summer's scorching heat waves in the U.S. and Europe, which killed hundreds, sparked wildfires and forced thousands of people to flee their homes, there's simply no way to ignore the grim reality: "The face of the dire impacts of climate change isn't disappearing polar bears or icebergs. It's us—human beings—our health, our



Smoke and soot from fires can worsen air quality thousands of miles away.

safety and our lives," says Dr. Renee Salas, Yerby Fellow at the Center for Climate, Health and the Global Environment (C-CHANGE) at the Harvard T.H. Chan School of Public Health, in Boston. "As an ER doctor, I'm trained to recognize emergencies, and the climate crisis is the biggest health emergency we're facing now and for the foreseeable future."

THE WEATHER PRESSURE COOKER

EWEs are among the most dangerous consequences of our changing climate. Burning fossil fuels releases carbon dioxide—a greenhouse gas that traps solar radiation—into the atmosphere. Trapped radiation increases global temperatures, which results in droughts, heat waves and wildfires; causes polar ice caps to melt and sea levels to rise, which increases flooding; and warms the ocean, which fuels, among other problems, the strength of hurricanes. As the Arctic warms, it also stretches the range of the polar vortex, a circular wind pattern, which produces extreme winter storms.

Graphic examples aren't hard to find. In February 2021, a snow and ice storm overwhelmed the power grid in normally temperate Texas, leaving millions without heat and causing 246 deaths, according to the Texas Department of State Health Services. In June 2021, scorching temperatures in Oregon, Washington and British Columbia, Canada, killed at least 600 people—and possibly far more, if unexpected "excess deaths" from cardiovascular and respiratory disease, both of which can be triggered by extreme heat, are taken into account.

EWE's also leave a slew of health problems in their wake. "Drought is a great example," says Salas. "It creates the conditions for mosquitoes to acquire West Nile virus from birds and spread it to people, it worsens asthma and other lung conditions, and it's associated with an increase in mental health problems, as are most natural disasters." Floods, the most common EWE, affect millions of people around the world, causing injuries and spreading waterborne diseases like hepatitis A and E. They also carry pathogens that cause diarrheal epidemics, which kill more than a million people around the globe annually, especially children.

More than a third of households in California that have been affected by wildfires reported the onset of serious health problems, according to a survey by NPR, Harvard University and the Robert Wood Johnson Foundation that was released in June this year—not surprising, since wildfire smoke contains microscopic particles, which can penetrate deep into the lungs, causing everything from asthma and coughing to blood clots and heart attacks. Researchers at the University of California at Davis reported in 2020 that wildfire smoke also causes inflammatory changes—even in healthy people—which increase the risk of developing lung disease.

Air pollution in general is notoriously harmful and worsens with rising temperatures, too, because heat-driven chemical reactions produce smog. "Air pollution kills

around 8.7 million people a year, and we can expect that to increase as the climate warms," says Salas. It raises the risk not only of asthma and lung disease but also breast and lung cancer and heart disease. And it increases the risk of dying from respiratory infections, including COVID-19.

A warming temperature can impact everyday health, too. "Warmer temperatures are increasing pollen counts and the length and severity of allergy season," says Dr. Kari Nadeau, a Naddisy Foundation endowed professor of medicine and pediatrics at Stanford University, in California. She and her colleagues published a study in 2021 which found that tree pollen and mold seasons in the San Francisco Bay Area expanded by a few days every year from 2002 to 2019.

In addition, says Dr. Aaron Bernstein, director of Harvard's C-CHANGE, the changing climate is shifting and expanding the range of disease-causing insects, from mosquitoes that spread malaria to ticks that cause Lyme disease. "Insects are cold-blooded, so they're fleeing the heat and turning up in places we've never seen them before," he says. Other animals that carry infectious diseases are migrating closer to large population centers due to habitat loss and climate change—and insects are biting them and spreading those diseases to people—a pattern that could result in more infectious disease epidemics, he adds. (For more on how climate change facilitates the spread of viruses, see page 81.)



Due to increasing droughts, wildfires are burning hotter.

THE HUMAN TOLL

The World Health Organization forecasts that between 2030 and 2050 climate change will cause approximately 250,000 additional deaths per year, from malnutrition, malaria, diarrhea and heat stress alone. Add in the other likely disasters, like food shortages, which can be caused by drought and floods, and the toll could be far more catastrophic.

"We need to blunt the worst effects of climate change by replacing fossil fuels with clean energy as quickly as possible—and simultaneously address how climate change is making it harder for people to stay healthy," says Salas.

Doctors and insurance companies also need to understand the health consequences of extreme heat and air pollution. "Health insurance could cover home air filtration systems for people with asthma who live in areas with wildfire smoke, for example," says Salas. "Hospitals need to be better prepared for extreme heat and cold and natural disasters. We did a survey of almost 800 global health care leaders and 70% in the U.S. said climate change-related issues, like lack of power and supply chain disruptions, are impairing their ability to deliver care. Interventions need to happen at every level—from patients to public health departments—and quickly."

Ginny Graves is a health writer based in Fairfax, California.



Paving the Way for Viruses

Bugs spread more widely and easily thanks to floods, drought, deforestation and more.

By Ginny Graves

In a quest to determine how SARS-CoV-2, the virus that causes COVID-19, infected its first victims, researchers from the University of California in San Diego and other institutions analyzed the genes of viral samples from very early in the pandemic. Their study, published in July, concluded that the virus was transmitted to people in November or December 2019 from live animals—probably ones sold at the Huanan Seafood Wholesale Market in Wuhan, China.

Animal-to-human transmission (known as zoonotic transmission) is a pandemic origin story that's all too familiar to virologists. It's how HIV, Zika, Ebola and any number of flu viruses gained a foothold in humankind. "With the exception of cholera, every pandemic of the last century was caused by the spillover of an infectious agent from animals to people—and climate change may increase the likelihood of spillover," says Dr. Aaron Bernstein, director of the Center for Climate, Health, and the Global Environment at the Harvard T.H. Chan School of Public Health.

Indeed, the annual probability of pandemics could triple in the coming decades, according to a 2021 study

ABOVE *Monkeypox is a zoonotic disease stemming from rodents.*



While climate change may render some parasites extinct, that can still have a negative effect on health.

in the *Proceedings of the National Academy of Science* journal of the National Academy of Sciences, which looked at past pandemic data as well as the rate of increase in zoonotic diseases associated with climate change.

"As the planet warms, many creatures, from insects to mammals, are migrating to escape the heat and coming into contact with other animals, which creates opportunities to spread into new hosts," explains Bernstein. "Animals also are settling closer to large population centers, where the risk of transmitting diseases to people is higher, and once a spillover event happens, disease spreads quickly because of population density and air travel. Due to climate change, the planet is like a giant snow globe that's being shook. As animals land in new places, we're more likely to be exposed to viruses and bacteria we've never seen before."

Deforestation—a key contributor to climate change—is adding to the problem of animal migrations. Africa's Ebola epidemic, for instance, occurred in part because bats, which carry the disease, were forced to move when the forests they lived in were cut down, says Bernstein. In fact, research published several years ago in the *Vector-Borne and Zoonotic Diseases* journal predicted that changes in the tropical and subtropical forests may be the largest driver of emerging infectious zoonotic diseases around the world.

TAKING FLIGHT

Many diseases, like Ebola and COVID-19, spread directly from animals to people, then jump quickly from human to human. Others are spread by insects or other bugs, which pick up viruses or bacteria from animals and transmit them to people. These so-called "vector-borne" diseases, like malaria, dengue, yellow fever and West Nile virus, aren't usually contagious—but when enough infected bugs bite enough people, they can cause widespread illness and death. And as insects and bugs migrate because of climate change, they expand the range of people they can infect, says David Ross, CEO and president of the Task Force for Global Health in Atlanta.

"Neglected tropical diseases, like river blindness, which is transmitted by black flies, and elephantiasis, which is transmitted by mosquitoes, used to be contained to the tropical zone, but we've starting seeing cases in Egypt, on the other side of the Sahara Desert," he says.



'WE'RE STARTING TO SEE TROPICAL DISEASES, SUCH AS RIVER BLINDNESS AND ELEPHANTIASIS, SHOW UP IN NONTROPICAL AREAS.'

—David Ross, CEO of the Task Force for Global Health

Black-legged ticks, for instance, which carry a number of illness-causing pathogens, including *Borrelia burgdorferi*, the bacteria that causes Lyme disease, and Powassan virus, which killed two people on the East Coast this year, are on the move, spreading from their usual northeastern U.S. habitat into Canada, says Bernstein. They're also moving west across the U.S.—and they're emerging earlier, lengthening tick season, and, as a result, having more opportunity to infect people.

Other factors associated with climate change can increase the risk of epidemics, too. Floods, which become more common as glaciers melt and sea levels rise, are associated with increases in airborne infections, like flu and respiratory syncytial virus, and mosquito-borne diseases, like dengue.

During droughts, viruses and bacteria can sicken people by polluting groundwater and surface water. What's more, researchers at the University of California in Santa Cruz found that droughts amplify the size of West Nile virus outbreaks, probably because infected birds congregate around dwindling water sources, making them easy prey for mosquitoes, which then transmit the virus to people. As droughts increase over the next 30 years, the number of serious cases of West Nile virus could nearly double, the researchers said.

There are things we can do to protect ourselves—and they would protect the planet, too, says Bernstein. "To stop viral spillover from animals, we need to preserve forests around the world and curtail the sale and trade of wild animals, like China did in response to COVID-19," he says. "We also need to do everything we can to limit further warming by vastly reducing greenhouse gas emissions. Doing so will not only reduce scenarios that promote the spread of pathogens but also decrease air and water pollution and improve human health, making us better able to cope with infectious diseases we might be exposed to. This is the best approach we have to address an array of the most pressing problems we're facing. We'd be nuts not to do it."



Climate-related changes affect the development of kids' lungs, intellectual ability and mental health.



FROM THE *TIME* VAULT

Children Bear the Brunt

The negative effects begin in utero and can last a lifetime.

By Tara Law

Climate change affects everyone, but especially children. Their small bodies—and the fact that they grow so rapidly—make them more vulnerable to toxins, pollution and other climate-change fallout. Over their lifetimes, kids also face greater exposure to the damage of climate change than adults.

A recent scientific review article published in the *New England Journal of Medicine* shows just how dangerous climate-related threats are to children's health. The researchers analyzed data about the specific effects of a rapidly warming planet and found that climate change harms children's mental and physical health from the time they are in the womb through childhood—with potentially lifelong effects. Socially and economically disadvantaged children are especially affected, but all children are at risk. "There is direct harm, now, to children's health—and certainly their future is being jeopardized in a major way," says study co-author Frederica Perera, PhD, director of the Columbia Center for Children's Environmental Health.

Policies that help shift countries away from fossil fuels to renewable, more efficient sources of energy are likely to improve kids' health, the study authors say. "We know how to do it; we know alternatives, and they're working in different countries," Perera says. "We just have to speed the process up…and put into effect the solutions we know work."

Here are three climate factors that threaten all children around the world, according to the new research.

POLLUTED AIR

Air pollution affects children's health in many ways. Through exposure to polluted air, children breathe in fine particulate matter created when cars, factories and other sources burn fossil

fuels. Air-pollution exposure to the fetus during a mother's pregnancy has also been linked to low birth-weight, premature births and stillbirths; scientists hypothesize that may be because air pollution can result in inflammation that makes it hard for nutrition to get to the fetus, says Dr. Aaron Bernstein, a pediatrician and director of the Center for Climate, Health, and the Global Environment at Harvard T.H. Chan School of Public Health (who was not involved in the recent study). "Particulate pollution is a source of infant death, including stillbirth and death in infancy," says Bernstein. Air pollution can also harm children's lung growth and functioning and put them at higher risk for conditions like respiratory infections, bronchitis and asthma.

Other research suggests that air pollution can adversely affect children's minds starting in utero. An expecting mother's exposure to air pollution particles "can be directly toxic to the developing brain" of her fetus, says Perera. "They are able to traverse the placenta." One research review published in *Cognitive and Behavioral Neurology* in 2020 includes numerous studies that link exposure to air pollution to lower cognitive function in children. Other research has found associations between exposure to pollution and symptoms of anxiety and depression.

LESS NUTRITIOUS FOOD

Climate change is undermining one of the central building blocks for growing children: healthy food. Extreme weather events that destroy food crops, including drought, flooding and higher temperatures, are becoming more common. These can drive up the price of food and make it scarcer. Even when kids have enough food, they still may not have adequate nutrients; emerging research shows that high carbon dioxide levels may make food less nutritious.

Getting enough calories and essential nutrients is central to ensuring kids grow up healthy. If kids are undernourished, "their brains don't develop normally," says Bernstein. "It affects every organ."

Global hunger is already very common, and experts predict it will get worse. In 2021, about 193 million people were acutely food insecure—which the United Nations defines as food inadequacy that endangers lives or livelihoods—and about 26 million children were suffering from wasting, a condition in which kids don't have enough weight for their height, according to the World Food Programme.



Poorer communities tend to have more air pollution.

MORE TRAUMA

A world altered by climate change is more dangerous for children. Famines, drought, and extreme weather events are becoming more common as a result of climate change, as are the violent interpersonal conflicts that such disasters tend to generate. For instance, climate change-driven drought is thought to have contributed to the outbreak of the 2011 war in Syria. On a hotter planet, children are more likely to be exposed to trauma, including displacement; globally, about 2.4 million children were displaced by natural disasters alone in 2021, according to UNICEF.

Living through major trauma as a child is thought to increase risk for both mental illnesses like depression as well as physical conditions such as cancer, asthma and stroke. Stress in expecting mothers can also harm their fetus' cognitive development.

"If your house gets burned down or flooded by a hurricane, if you're impoverished because your family's livelihood has been destroyed by drought—these are adverse childhood events," says Bernstein, "and they can accumulate and exact harms across the lifespan."

—*Excerpted from* TIME, *June 17, 2022*



FROM THE *TIME* VAULT

What Extreme Heat Does to the Body

ORGANS AND TISSUES AREN'T DESIGNED TO WITHSTAND HIGH TEMPERATURES.

Heat waves kill more people annually in the U.S. than hurricanes, lightning, tornadoes, floods and earthquakes combined. Yet few people really understand how heat affects the body.

When our surroundings exceed the normal body temperature of 98.6F, the only way to keep from overheating is by sweating—the beads of water evaporating cause a cooling effect. But when humidity is high, sweating becomes less effective because the air is already saturated with moisture. The body can't cool down so your core temperature increases, triggering a series of internal emergency protocols to protect vital functions.

Blood flow to the skin increases, straining the heart. For every 1°F rise in core temperature, a typical person's heartbeat goes up 10 beats per minute, resulting in a racing pulse and a sense of light-headedness. The brain tells the muscles to slow down, causing fatigue. Nerve cells misfire, leading to headache, nausea or even vomiting. Excessive sweating throws your electrolytes out of whack and can cause cramping. This is the beginning of heat exhaustion, and if it is not treated with shade, rest and some kind of electrolyte replacement, it can quickly veer into dangerous territory. If the core temperature continues to rise past 104°F, organs start shutting down and cells deteriorate. An overtaxed heart can go into cardiac arrest. This is heat stroke.

Camilo Mora, PhD, an associate professor at the University of Hawaii at Manoa's geography department, describes 27 different ways the body succumbs to overheating, from kidney failure to blood poisoning when the gut lining disintegrates. Mora's research has made him understand deeply how awful the impacts of heat on the human body can be. "Dying of heat stroke is sometimes better than surviving," he says. "People have to realize how serious extreme heat is." *—Aryn Baker, excerpted from* TIME*, June 13, 2022*

The Missing Link: Equity

Medicine is only one part of making people healthier.

By Janet Lee

Doctors perform a variety of tasks every day to improve their patients' health. They might set a broken bone, assess a heart condition, prescribe medication for diabetes, perform a colposcopy to diagnose HPV or consult about how to treat someone with lung cancer (among many other things). But how much do these tasks really improve health? All of these things can be exacerbated by factors at home or in their environment that the patients have little to no control over.

"Social science tells us that medical care contributes only 15 to 20% to health," says Philip Alberti, PhD, senior director of health equity research and policy for the Association of American Medical Colleges (AAMC) and the founding director of the AAMC Center for Health Justice. Other, often ignored contributors include what are called social determinants of health, such as race and ethnicity, lifestyle habits, socioeconomic factors (education, employment, income) and environment, to name a few.

These social determinants of health can contribute to health inequities: People, whether due to race, ethnicity, gender, sexuality or disability, don't have the same opportunities to be their healthiest because of racism; lack of transportation; reduced access to affordable, nutritious foods; jobs that require them to work in unhealthy environments; or unsafe living environments.

"There are well documented inequities along the whole trajectory within health care," says Alberti. "There are racial, social and economic inequities, from premature birth to premature death." The lack of equity is what keeps maternal mortality rates in the U.S. at the bottom when compared to other high-income countries. It's what makes life expectancy in the U.S. lower than other developed countries, despite outspending everyone else on medical care. It's what led to Black and Hispanic people being hospitalized and dying from COVID-19 at far higher rates than white people early on in the pandemic. It's what keeps Black men in New York City from having the same access to the monkeypox vaccine as men in other racial groups, according to data released in August from New York City's health department. While they make up 31% of the at-risk population, they only received 12% of distributed doses to date.

A 2022 study, the first of its kind to look at the relationship between health-related social needs and emergency department (ED) use, found that having multiple social needs, such as difficulty paying utility bills or a lack of transportation, was strongly associated with the risk of having two or more ED visits during the prior year. Those with four or more needs had a tenfold higher risk of ending up in the ED. The study was conducted in the Houston area and published in the *Journal of General Internal Medicine*.



The infant mortality rate of Black babies is more than twice that of white babies.

MAKING PROGRESS

Although the first research reviews on the impact of racism on health were done in the mid-1990s (they showed an adverse effect), there's been a huge push over the last several years to better understand the social and structural determinants of health. Medical schools, hospitals, insurers and policymakers—the different groups responsible for delivering health care in the U.S.—are acknowledging health inequities and figuring out how best to address them. The following are some of the areas that may provide fertile ground for progress.

Community Engagement Hospitals, in particular, can't ignore the communities they serve. "We know that health is determined by what happens in the community. Those things aren't random; they're the result of structural racism and the social determinants of health," says Dr. John A. Rich, director of the Rush BMO Institute for Health Equity in Chicago.

Rush University System for Health is, in fact, a great example of how a medical system can embed itself in the community, helping to address those social and structural determinants of health. In 2016, Rush implemented a health equity strategy that centered around its local community. The goal: to address health inequities in their neighboring West Side communities—approximately half a million people—that were contributing to a startling 14-year life expectancy gap between those areas and more white, affluent areas. They wanted to reduce that gap by at least 50% by the year 2030.

The Rush Model

CREATING A BLUEPRINT FOR OTHER HOSPITALS.

Here are some of the ways the hospital system approaches its mission to improve health and health equity.

COMMUNITY CLINICAL PRACTICE Within the community, Rush and its partners provide postpartum home visits, run school-based health centers and more.

COMMUNITY ENGAGEMENT Besides treating patients, Rush helps provide free meals to residents in need, hires locally and offers paid high school and college internships.

HEALTH EQUITY RESEARCH Rush and the University of Chicago received an NIH grant to establish a Center for Multiple Chronic Diseases Associated With Health Disparities.

POLICY AND ADVOCACY Rush has partnered with other local hospitals as well as with city government and other community groups.

EDUCATION AND WORKFORCE ENGAGEMENT Rush educates medical students about health equity and social determinants of health.



Reprinted with permission of Rush University System for Health.

In addition to establishing community-based clinics, the plan called for hiring, purchasing, investing and volunteering locally. Everything the medical center did was through the community lens.

Because of the ways Rush (along with other partners in the area) has infiltrated the community, at the height of the pandemic, Chicago, which is the third largest city in the U.S., had the seventh highest mortality rates, says Dr. David Ansell, senior vice president for community health equity at Rush. (For a closer look at the Rush plan, which was featured in *New England Journal of Medicine Catalyst Innovations in Care Delivery* in 2021, see sidebar, left.)

"There's no health equity program that will be successful if the community that it affects is not involved," shares Seun Ross, DNP, director of health equity at Independence Blue Cross in Philadelphia.

Training at Schools Besides teaching medical students about the importance of social determinants of health and how to screen for them (if clinicians can't collect the data about the determinants, they don't know what the contributing factors are), medical schools and other training programs should be diverse as well, says Dr. Michelle Albert, president of the American Heart Association and admissions dean at the University of California, San Francisco. "We need to double down on having a workforce that's representative of the demographics of the community so they can understand the lived experiences of the population they're treating," says Albert. "That's really important. Having that understanding will engender research, care and the clinical concordance [incorporating the wishes and beliefs of the patient] that's needed to address equitable health care."



According to the Association of American Medical Colleges, the incoming medical school class of 2021–2022 was the most diverse ever.

Digital Health Patients' access to a computer, the internet or a smartphone will determine how well they can engage with their health care in this new digital era, says Ross. "I think it's incumbent on all of us to do our due diligence and ensure these new tools are assisting in closing disparities and not exacerbating them," she adds. "Algorithmic bias is a real thing. We have to ensure that any biases that are already embedded in data are not used to perpetuate them." Ross gives an example of how bias creeps into data: "Let's say I'm a product developer and I want to develop a tool that can help increase access to psychiatrists. If I use the data that shows Black people are disproportionately diagnosed with schizophrenia and bipolar disorder as part of my algorithms, I'll continue to perpetuate that false idea. The app will send Black users to providers who specialize in those conditions." In that case, the algorithms developers use can widen the divide between groups.

Policymaking From the American Medical Association and the National Academy of Medicine to the Centers for Disease Control and Prevention and the Center for Medicare & Medicaid Services (CMS), key groups are stoking the momentum that's started to build and analyzing what laws, rules, regulations and organizational structures need to change to promote health equity. In 2021, the CMS issued guidance to states that encourages them to adopt strategies to address social determinants of health in the Medicaid and Children's Health Insurance Program as a way to improve health outcomes and reduce costs.

"Health and health equity are not zero-sum games," says Albert. "It's not about taking from community A and giving to community B. Our challenge in the next few years is to do a better job of communicating that. A lot of awareness has been raised and that gives me optimism."



A reported case of polio in New York was in a man who had recently traveled to Hungary and Poland.

Why Global Health Is the New Public Health

What happens in any given part of the world has huge implications thousands of miles away—and vice versa.

By Ginny Graves

From early May, when most Americans first heard the word monkeypox, until July 23, when the World Health Organization declared the outbreak a "public health emergency of international concern," cases soared to more than 16,000 in 75 countries—most of which had not previously seen the virus. By Aug. 17, there were 32,000 cases; Spain, Brazil and India had reported the first monkeypox deaths outside of Africa, where the virus first appeared in 1970; and infections showed few signs of slowing as countries struggled to contain the unfamiliar contagion.

"These days, an infectious disease can spread around the world in a matter of hours," says Dr. Ingrid Katz, associate faculty director of the Harvard Global Health Institute. "Thanks to air travel and the interconnectedness of commerce and economies, what affects one country affects us all, whether it's a virus or a decrease in childhood vaccinations. When it comes to health, no country exists in isolation."

Since public health goes way beyond national borders, it's important to know how experts are prioritizing global concerns. These are some of the biggest issues facing global health organizations in the coming decades.

RECOGNIZING—AND CURTAILING—PANDEMICS

The World Health Assembly, the decision-making body of the World Health Organization, is in the midst of drafting an international agreement to strengthen pandemic prevention, preparedness and response around the world. If countries can agree to terms, international pandemic threat detection and response treaties would pave the way for every country to have a trained workforce of field epidemiologists—essentially international disease detectives—and bolster disease surveillance systems and laboratory and diagnostic capabilities, says David Ross, CEO and president of the Task Force for Global Health in Atlanta.

Among the thorny issues: Deciding the most effective way—perhaps with incentives—to encourage countries to report outbreaks immediately. "Even minor reporting delays can make a big difference in how widely an infectious disease spreads, and as it stands now, there are disincentives to reporting, like travel bans, which hurt countries' economies," says Ross.

At the same time, the U.S. Centers for Disease Control and Prevention is expanding its work around the globe to improve outbreak detection, reporting and response. "We have offices in more than 50 countries, where CDC scientists and local staff work with the ministries of health of the host nation to build those skills—efforts

that paid off during COVID," says Dr. Kevin Cain, principal deputy director of the CDC's Center for Global Health. "The places we really invested in were far more likely to detect outbreaks and report them quickly. Our staff around the world, who are mostly citizens of the country they live in, did heroes' work. They helped their local ministries of health respond to the crisis at a time when we couldn't send many people to help."

DEVELOPING AND DISTRIBUTING VACCINES

"We learned during COVID that even new diseases can become vaccine preventable fairly quickly—but vaccines don't do any good sitting in vials," says Cain. "We need to get shots into arms, so improving distribution is critical." Just 20% of people in low-income countries have received a single dose of the COVID-19 vaccine, and 10 states in the U.S. have full vaccination rates below 57%. With large swaths of unvaccinated people, whether due to lack of access or misinformation, viruses have ample opportunity to spread and mutate—one reason the world is still dealing with new variants of COVID-19. "We're trying to help countries communicate more effectively about the benefits of vaccines," says Cain.

One potential solution for making vaccine distribution simpler is helping countries around the world build their own capacity to manufacture and distribute shots, says Katz. "Africa, Brazil and India are already doing it, but it needs to happen far more broadly," she says. "For too long, we've treated vaccines as a market commodity rather than a public good. Companies have to be willing to waive patents and share information and raw materials to ensure the majority of people are vaccinated."

At the same time, global health experts have sounded the alarm on the need to redouble efforts on childhood vaccinations. In July, the WHO and UNICEF announced the largest sustained decline in childhood vaccinations in 30 years. For instance, about 25 million children missed one or more doses of the vaccine against diphtheria, tetanus and pertussis in 2021. "That's because of COVID, which consumed the health work force," says Stephen Morrison, director of the Global Health Policy Center at the Center for Strategic & International Studies. "Now the priority is learning to walk and chew gum at the same time—to prepare and respond to pandemics and renew and revitalize all the great work that's been done with childhood vaccines for 30 years. We're likely to see an uptick in cases and deaths from formerly well-controlled diseases unless we get the vaccination rates up to where they need to be."

It's already happening with polio, which most countries, except for Pakistan and Afghanistan, had largely eradicated. After the Global Polio Eradication Initiative paused its immunization campaign in 2020, there was an outbreak in Malawi in late 2021. In June 2022 the United Kingdom had its first outbreak in 40 years. And in July, an unvaccinated man in New York was diagnosed with the disease and suffered paralysis. The virus has since been detected in wastewater in New York City and elsewhere in the state.

Migrants and Refugees Are Among the Most Vulnerable

A HUGE PORTION OF THE WORLD'S POPULATION IS ON THE MOVE—WITH THEIR HEALTH AT RISK.

There are roughly 1 billion migrants around the world—one in eight people—according to a July World Health Organization report. "The migratory process exposes people to deprivation, overcrowding and lack of access to nutrition and basic health services," says Dr. Santino Severoni, director of the health and migration program at the WHO. "A meta-analysis in Europe showed that migrant mothers had double the risk of mortality during and after pregnancy. And when you're living in poor conditions...and separated from your family and community, depression, anxiety and PTSD are common."

In 2019, the WHO developed a global action plan with six key priorities, including mainstreaming refugee and migrant health into global, regional and national agendas, and promoting continuity of essential health care. The program has been ongoing throughout the pandemic. "Migrants are excluded from access to health systems, even though preventive health care is far more cost effective than treating sick people after the fact," says Severoni. "Commitment to a universal health care approach is essential."



South Sudan (shown), Yemen and Afghanistan, among other countries, are considered extreme hunger hot spots, per Oxfam.

ADDRESSING HUNGER AND POVERTY

According to the State of Food Security and Nutrition in the World 2022 report, published by the Food and Agriculture Organization of the United Nations (FAO), as many as 828 million people went hungry in 2021, an increase of 150 million since the beginning of the pandemic. "Hunger is a huge issue, and it's getting bigger every day," says Emily Janoch, senior director of learning at CARE, an international humanitarian organization fighting world hunger and poverty. "Every country has pockets of hungry people, but the pandemic, the war in Ukraine and the climate crisis have exacerbated those problems." People are facing famine and starvation in Yemen, Somalia, Ethiopia and Afghanistan, for instance, which relied heavily on Russian and Ukrainian imports of grain, cooking oil and fertilizer.

It's not only heartbreaking; it's dangerous. Malnourished people are more vulnerable to infectious disease and are less able to contribute to the economy, which destabilizes countries' workforces and threatens their economic stability. As a result, it undermines their ability to implement effective public health campaigns, from nutrition initiatives to vaccine distribution.

At the 2021 Tokyo Nutrition for Growth Summit, the U.S. committed up to $11 billion to fight malnutrition around the world. It also launched the Global Nutrition Coordination Plan, which has six priorities, including women's nutrition before and during pregnancy and breastfeeding; prevention and management of wasting in children younger than 5; and ensuring people get sufficient micronutrients in their diet.

"We also need to invest in the farmers themselves—especially women farmers. They make up nearly half of all agricultural labor around the world, but they often don't have decision-making power, access to proper tools, seeds or fertilizers, or rights to their land," adds Janoch. If women had the same access to agricultural resources as men, production on women's farms in developing countries could increase by 20 to 30%, according to a report by the FAO.

IMPROVING THE QUALITY OF HEALTH CARE AND TECHNOLOGY

Poor quality health care in low- and middle-income countries results in an estimated 8.4 million deaths per year and as much as $1.6 trillion in lost productivity, but artificial intelligence (AI) could be an effective way to address the knowledge and judgment gaps that cause the most problems, says Katz.

To realize AI's full promise in the realm of global health requires reliable, high-quality data, so AI is trained to make the best choices and has the capacity to oversee and manage the rapidly changing technology, says Katz. "Used effectively, AI has the potential to revolutionize global health and health care."

In countries like Ethiopia or Nigeria, where the ratio of doctors to the overall population is the lowest in the world, health professionals, especially in rural areas, often function on their own, without the help of specialists or pharmacists. They also have to provide a wide range of services, reducing the quality of care. AI systems can support physicians in diagnosing patients and choosing treatment plans—which can often reduce the unnecessary use of antibiotics—and in some cases, AI could even stand in for a human doctor if none are available.

Straight Talk

Experts weigh in on the future of medicine and health care.

'A viral threat anywhere in the world is a threat to everyone, including everyone in the United States.'

—Dr. Kevin Cain, acting director of the CDC's Center for Global Health

'A lifestyle medicine practitioner can help guide people to eat or exercise a certain way or to be more mindful. When combined with precision medicine, the patient will be given a system to help their physiology not manifest all the things [i.e., genetic predispositions] they've inherited.'

—Dr. Raja Jaber, director of the Lifestyle and Integrative Medicine Program at the Renaissance School of Medicine at Stony Brook University

'Eventually, doctors will adopt AI and algorithms as their work partners. This leveling of the medical knowledge landscape will ultimately lead to a new premium: to find and train doctors who have the highest level of emotional intelligence.'

—Dr. Eric Topol, author of *Deep Medicine: How Artificial Intelligence Can Make Healthcare Human Again*

'If we fail to act on climate change, it will erode the foundations of health we all take for granted: clean air, clean water, nutrient-rich food and access to high-quality health care.'

—Dr. Renee Salas, Yerby Fellow at the Center for Climate, Health, and the Global Environment at the Harvard T.H. Chan School of Public Health

‘Global health security is constrained by a dangerous cycle, where periods of crisis are followed by periods of complacency. We can no longer afford to be complacent.’

—Stephen Morrison, director of the Global Health Policy Center at the Center for Strategic & International Studies

‘You can tell people to make healthy lifestyle choices, but one of the root causes of health inequities is economic adversity. We have to focus on this. Within the American Heart Association, we’re addressing economic adversity as a root driver of poor health, especially cardiovascular health.’

—Dr. Michelle Albert, president of the American Heart Association

‘[Precision medicine] is going to be completely unprecedented. It’s going to affect medicine in ways we’ve never seen before.’

—Tom Maniatis, PhD, director, Columbia University Precision Medicine Initiative

‘The impact for society at large from Long COVID is going to be huge. Millions of people will be affected, as well as the labor market, marriages and relationships. It has wide ramifications on people’s lives.’

—Dr. Ziyad Al-Aly, a clinical epidemiologist at Washington University and chief of the research and education service at Veterans Affairs St. Louis Health Care System

‘I’ve studied some of the world’s longest-lived populations and it is through powerful choices that we can activate the biology of longevity. We are not fated to simply just extend lifespan, without… enjoying and celebrating life itself. We can do both.’

—Dr. Kien Vuu, assistant professor of health sciences at UCLA and author of *Thrive State: Your Blueprint for Optimal Health, Longevity, and Peak Performance*

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Artificial intelligence in medicine isn't some far-off sci-fi plot: It's improving health care right now.